British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN

Final

Asthma: diagnosis, monitoring and chronic asthma management (update)

[Q] Evidence reviews for drug combinations and sequencing for asthma management

BTS/NICE/SIGN collaborative guideline NG245

Evidence reviews underpinning recommendations 1.7.3, 1.7.4, 1.7.5, 1.7.6, 1.7.7, 1.8.2, 1.8.3, 1.8.4, 1.8.5, 1.8.6, 1.8.7, 1.9.5 and 1.9.6 in the guideline

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Developed by BTS, NICE and SIGN

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1. Drug combinations and sequencing for asthma management

1.1 Review question

What is the most clinically and cost-effective sequence in which to introduce additional drugs or combination of drugs for the management of asthma when initial management fails to provide adequate control?

1.1.1 Introduction

When initial management does not fully control a person's asthma, even after fundamental factors such as inhaler technique are addressed, step-up therapy is needed. There are several treatment options including escalating the dose of inhaled corticosteroid (ICS) or adding in additional medicines such as a long-acting beta-agonist (LABA), a leukotriene antagonist (LTRA) or a long-acting anti-muscarinic agent (LAMA). Step-up therapies can increase the burden of treatment for people with asthma and may have side-effects. It is therefore important to understand the evidence around which of these treatments is most likely to be effective and safe, and in which order they should be added to give the best chances of achieving maximum benefit.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

This review was split into two separate questions for the adults and young people population. This approach was taken to formulate separate recommendations depending upon the current treatment status of the individual, with current treatment dictating the step-up options available. Step 3.2A covers adults and young people who at recruitment had asthma that was uncontrolled whilst receiving as-needed (referred to as prn) SABA, prn ICS/formoterol or regular low-dose ICS. There were four treatment combinations in this population: regular low-dose ICS with prn SABA or prn ICS/formoterol, and low-dose ICS/LABA with prn SABA or prn ICS/formoterol (likely to be MART but could have been one ICS/LABA combination with ICS/formoterol as the reliever medication). Data was only expected on three out of four of the listed interventions (regular low-dose ICS with ICS/formoterol prn was unlikely to be included in studies due to the main benefit of ICS/formoterol prn being the use of a single inhaler for maintenance and relief (MART), which is made redundant if an ICS-only containing inhaler is used for maintenance):

- Regular low-dose ICS with SABA prn
- Regular low-dose ICS/LABA with SABA prn
- Regular low-dose ICS/LABA with ICS/formoterol prn

Step 3.2B covers adults and young people who at recruitment had asthma that was uncontrolled whilst receiving regular ICS or regular ICS/LABA with either SABA or ICS/formoterol prn. In this review there were six maintenance treatment options, each of which were divided depending upon the reliever medication use, that being SABA or ICS/formoterol. Data for ICS/formoterol as the reliever medication was only expected for interventions containing ICS/formoterol as the maintenance medication for the same reasons as outlined in 3.2A.

Table 1: PICO characteristics of review question

Population	Inclusion: People with a diagnosis of asthma that is not controlled by initial treatment Separate review questions for: • Adults and young people (≥12 years) Stratified based on initial treatment: ICS/Formoterol (as needed) vs regular low-dose ICS vs SABA (as needed) • Children 5-11 years • Children under 5 years • Exclusion: People diagnosed with asthma who are treatment naïve • People who have received additional drugs other than ICS or ICS/LABA • People with severe asthma
Interventions	**Maintenance therapies** <u>Step 3.2A : People ≥12 years (with asthma that is uncontrolled with as-needed SABA, ICS/formoterol or regular-low dose ICS)</u> **All treatment options for this population should be grouped depending upon the as-needed (prn) medication** **1) ICS/formoterol maintenance and reliever therapy (MART)** **2) SABA** • Regular low dose ICS (as defined in the NICE table) (budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone) **/** LABA (formoterol, salmeterol, vilanterol or indacaterol) combination inhaler or concurrent inhalers • Regular low dose ICS inhaler <u>3.2B: People ≥12 years (with asthma that is uncontrolled with regular ICS, regular ICS/LABA or ICS/formoterol MART)</u> **All treatment options for this population should be grouped depending upon the as-needed (prn) medication** **1) ICS/formoterol maintenance and reliever therapy (MART)** **2) SABA** • Regular moderate/high dose ICS/LABA (formoterol, salmeterol, indacaterol or vilanterol) combination inhaler or concurrent inhalers • Regular low/moderate dose ICS/LABA combination inhaler plus montelukast • Regular low/moderate dose ICS/LABA combination inhaler plus LAMA • Regular moderate/high dose ICS inhaler • Regular low/moderate dose ICS inhaler plus montelukast • Regular low/moderate dose ICS inhaler plus LAMA • ICS/SABA combination inhaler prn <u>Children 5-11 years</u> • Regular paediatric moderate dose ICS/LABA with SABA prn • Regular paediatric moderate ICS and montelukast with SABA prn • Regular paediatric moderate/high dose ICS with SABA prn • ICS/formoterol maintenance and reliever therapy (MART) <u>Children under 5 years (initial treatment: daily ICS)</u>

	Step2 • Moderate dose regular ICS • Intermittent montelukast • Regular montelukast • Regular moderate/high dose ICS/LABA combination • Intermittent increases in ICS dose
Comparison	Interventions compared to one another
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at 3-5 months and ≥6 months) • Severe exacerbation rate (event rate per person year) • Mortality (dichotomous outcome at ≥6 months) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months) • Asthma control assessed by a validated questionnaire (ACQ/p ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) • Hospital admissions (dichotomous outcome at 3-5 months and ≥6 months) • Reliever/rescue medication use (continuous outcome at ≥3 months) • Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). *Note: For children, only use FEV1 %pred* • Adverse events (general adverse events minus specific event listed below if reported): ○ Linear growth (continuous outcome at ≥1 year), ○ Pneumonia frequency (continuous outcome at ≥3 months), ○ Adrenal insufficiency (as defined by study, including short synacthen test and morning cortisol, dichotomous outcome at ≥3 months) ○ Bone mineral density (continuous outcome at ≥6 months) • Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks
Study design	• RCTs • Systematic reviews of RCTSs Exclusion: • Studies <12 weeks

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Fifteen randomised controlled trials and one post-hoc analysis of three RCTs (16 papers) were included in review question 3.2a (first add-on treatment) of adult and young people ≥12

years studies (Atienza, et al., 2013, Bailey, et al., 2008, Boonsawat, et al., 2008, Jenkins, et al., 2017, Kornmann, et al., 2020, Kuna, et al., 2006, Lalloo, et al., 2003, Murray, et al., 2004, Nathan, et al., 2012, Nelson, et al., 2003, Pearlman, et al., 2013, Pearlman, et al., 2004, Rabe, et al., 2006, Rabe, et al., 2006, Renzi, et al., 2010, Strand, et al., 2004); these are summarised in Table 2 below.

Fifty-one randomised controlled trials were included in review question 3.2b (further step-up treatment) of adults and young people ≥12 years studies (Barnes, et al., 2007, Bateman, et al., 2004, Bateman, et al., 2011, Bateman, et al., 2014, Beasley, et al., 2015, Bernstein, et al., 2015, Bleecker, et al., 2014, Bousquet, et al., 2007, Buhl, et al., 2012, Busse, et al., 2013, Corren, et al., 2013, Emami, et al., 2014, Fish, et al., 2001, Hoshino, et al., 2019, Huchon, et al., 2009, Ind, et al., 2003, Jenkins, et al., 2000, Juniper, et al., 2002, Katial, et al., 2011, Kerstjens, et al., 2015, Kerstjens, et al., 2020, Kerwin, et al., 2011, Kuna, et al., 2007, Lee, et al., 2020, Lin, et al., 2015, Lin, et al., 2019, Mitchell, et al., 2003, Nabil, et al., 2014, Noonan, et al., 2006, O'Byrne, et al., 2005, O'Byrne, et al., 2014, Paggiaro, et al., 2016, Price, et al., 2003); (Patel, et al., 2013, Pavord, et al., 2009, Pertseva, et al., 2013, Peters, et al., 2008, Price, et al., 2011, Scicchitano, et al., 2004, Shapiro, et al., 2000, Sher, et al., 2017, Spector, et al., 2012, Stirbulov, et al., 2012, Takeyama, et al., 2014, van Zyl-Smit, et al., 2020, Virchow, et al., 2019, Vogelmeier, et al., 2005, Wallin, et al., 2003, Wang, et al., 2015, Ye, et al., 2015, Zangrilli, et al., 2011, Zetterstrom, et al., 2001) these are summarised in table 3 below. Eight were included in the review of studies in children aged 5-11 years (Berger, et al., 2010, Bisgaard, et al., 2006, de Blic, et al., 2009, Lenney, et al., 2013, Malone, et al., 2005, Morice, et al., 2008, Pearlman, et al., 2017, Vaessen-Verberne, et al., 2010) these are summarised in table 4 below. Two were included in the review of studies in children under 5 years (Fitzpatrick, et al., 2016, Szefler, et al., 2013); these are summarised in table 5 below. Evidence from these studies is summarised in the clinical evidence summary tables 6 to 26.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Adults and young people ≥12 years

Table 2: Summary of studies included in the evidence review for first add-on treatment for adults and young people ≥12 years with uncontrolled asthma (review 3.2a)

Study	Intervention and comparison	Population	Outcomes	Comments
Atienza 2013 (Atienza et al., 2013)	**Low dose ICS/formoterol maintenance and reliever therapy (MART)** (160/4.5 mcg BUD/FORM twice daily plus additional inhalations as-needed)	2091 people aged ≥16 years receiving regular ICS (mean dose ~660 mcg/day) for at least 3 months and using as-needed medication on ≥5 out of 7 days of the run-in period	Severe asthma exacerbations Severe exacerbation rate Mortality Asthma control Adverse events	Funded by AstraZeneca Downgraded by one increment due to population indirectness – participants were receiving moderate-dose, not low-dose ICS at screening

Study	Intervention and comparison	Population	Outcomes	Comments
	Regular low dose ICS/LABA (160/4.5 mcg BUD/FORM twice daily plus 0.4 mg terbutaline as-needed) 52 weeks	Exacerbations: Yes – at least one in the past year Atopy: Not reported International		
Bailey 2008 (Bailey et al., 2008)	**Regular low dose ICS/LABA** (50/100 mcg SAL/FP twice daily) **Regular low dose ICS** (100 mcg FP twice daily) 52 weeks	475 African American people aged 12-65 years Symptomatic whilst receiving 200 mcg FP equiv. (SABA use and symptom score ≥2 on ≥4 of 7 days of the run-in Exacerbations: not reported Atopy: not reported USA	Severe asthma exacerbations Severe exacerbation rate Hospital admissions (due to asthma) Reliever/rescue medication use Lung function (FEV1 and PEF)	Funded by GlaxoSmithKline Downgraded by one increment due to population indirectness – participants randomised after achieving asthma control during run-in period, therefore not necessarily representing a population with asthma that is uncontrolled
Boonsawat 2008 (Boonsawat et al., 2008)	**Regular low dose ICS/LABA** (50/100 mcg SAL/FP once daily) **Regular low dose ICS** (100 mcg FP once daily) 12 weeks	303 people aged 12-79 years receiving SABA monotherapy Daytime symptom score ≥1 on ≥3 of the last 7 days Exacerbations: not reported Atopy: not reported Multinational	Severe asthma exacerbations Severe exacerbation rate	Funded by GlaxoSmithKline
Jenkins 2017 (Jenkins et al., 2017)	**Low dose ICS/formoterol maintenance and reliever therapy (MART)** (160/9 or 320/9 mcg BUD/FORM plus additional as-needed) **Regular low/moderate**	1239 People aged 12-80 years who used ≥7 inhalations of SABA during the final 7 days of the run-in Post-hoc analysis including only participants who were receiving	Reliever/rescue medication use Lung function (FEV1)	Funded by AstraZeneca Downgraded by one increment due to intervention indirectness – post-hoc analysis included three studies, two of which used moderate-dose

Study	Intervention and comparison	Population	Outcomes	Comments
	dose ICS (320 or 640 mcg BUD per day plus terbutaline as-needed) 6-12 months (varied between included studies)	low-dose ICS (<400 mcg BUD) at screening Exacerbations: not reported Atopy: not reported Multinational		ICS or ICS/LABA combinations secondary publication of Rabe 2006 (included in this review), Scicchitano 2006 and O'Byrne 2005 (included in 3.2b))
Kornmann 2020 (Kornmann et al., 2020)	**Regular low dose ICS/LABA** (150/80 mcg MF/IND once daily) **Regular low dose ICS** (200 mcg MF once daily) 12 weeks	802 people aged 12-75 years with an ACQ score >1.5 and FEV1 <90% of predicted Exacerbations: mixed – 80% with none, 18% with one and 2% with more than one in the past year Atopy: not reported Multinational	Severe asthma exacerbations Mortality Hospital admissions Asthma control Lung function (PEF and FEV1)	Funded by Novaritis
Kuna 2006 (Kuna et al., 2006)	**Regular low dose ICS/LABA** (80/4.5 mcg BUD/FORM either once or twice daily (two study arms combined) **Regular low dose ICS** (200 mcg BUD once daily) 12 weeks	616 people aged 18-80 years with asthma that was not optimally controlled on 200-500 mcg daily ICS and an FEV1 <90% Exacerbations: not reported Atopy: not reported Multinational	Reliever/rescue medication use Lung function (PEF) Pneumonia (RTIs)	Funded by AstraZeneca
Lalloo 2003 (Lalloo et al., 2003)	**Regular low dose ICS/LABA** (80/4.5 mcg BUD/FORM twice daily) **Regular low dose ICS** (200 mcg BUD twice daily) 12 weeks	467 people ≥18 years of age with asthma not fully controlled on 200-500 mcg daily ICS Exacerbations: not reported Atopy: not reported Multinational	Severe asthma exacerbations Pneumonia (RTIs)	Funded by AstraZeneca

Study	Intervention and comparison	Population	Outcomes	Comments
Murray 2004 (Murray et al., 2004)	**Regular low dose ICS/LABA** (100/50 FP/SAL twice daily) **Regular low dose ICS** (100 mcg FP twice daily) 12 weeks	177 people aged ≥12 years receiving SABA, requiring ≥12 inhalations in the last 7 days or a symptom score ≥7 in this period Exacerbations: mixed Atopy: not reported USA	Severe asthma exacerbations Reliever/rescue medication use Lung function (PEF and FEV1)	Funded by GlaxoSmithKline
Nathan 2012 (Nathan et al., 2012)	Regular low dose ICS/LABA (100/10 FP/FORM twice daily) Regular low dose ICS (100 mcg FP twice daily) 12 weeks	237 people aged ≥12 years receiving ICS <500 mcg per day or SABA alone with ≥2 SABA uses and symptoms on ≥3 of any 7 consecutive days during the run-in Exacerbations: mixed Atopy: not reported USA, Canada and Ukraine	Severe asthma exacerbations Mortality Reliever/rescue medication use Lung function (FEV1)	Sponsored by SkyePharma
Nelson 2003 (Nelson et al., 2003)	**Regular low dose ICS/LABA** (44/21 mcg FP/SAL, two inhalations twice daily) **Regular low dose ICS** (44 mcg FP, two inhalations twice daily) 12 weeks	192 people aged ≥12 years treated with SABA alone, a symptom score ≥7 during the run-in period and an FEV1 <85% of predicted Exacerbations: mixed Atopy: not reported USA	Reliever/rescue medication use Lung function (FEV1 and PEF)	Funded by GlaxoSmithKline
Pearlman 2013 (Pearlman et al., 2013)	**Regular low dose ICS/LABA** (50/5 mcg FP/SAL, two inhalations twice daily)	238 people either receiving <500 mcg FP daily, or no ICS in the past 12 weeks, with ≥2	Severe asthma exacerbations Mortality Reliever/rescue medication use	Funded by SkyePharma

Study	Intervention and comparison	Population	Outcomes	Comments
	Regular low dose ICS (50 mcg FP, two inhalations twice daily) 12 weeks	SABA inhalations on any 3 of 7 consecutive days during the run-in period Exacerbations: none within a year Atopy: not reported North America		
Pearlman 2004 (Pearlman et al., 2004)	**Regular low dose ICS/LABA** (88/42 mcg FP/SAL twice daily) **Regular low dose ICS** (88 mcg FP twice daily) 12 weeks	181 people aged ≥12 years receiving low-dose ICS and/or SABA with an FEV1 <85% of predicted Exacerbations: not reported Atopy: not reported USA	Reliever/rescue medication use Lung function	Funded by GlaxoSmithKline
Rabe 2006 (Rabe et al., 2006)	**Low dose ICS/formoterol maintenance and reliever therapy (MART)** (80/4.5 mcg BUD/FORM, two inhalations once daily plus additional inhalations as-needed) **Regular low dose ICS** (160 mcg BUD, two inhalations once daily) 6 months	697 people aged 12-80 years receiving 200-500 mcg ICS per day who used ≥7 SABA inhalations during the last 10 days of the run-in period Exacerbations: not reported Atopy: not reported Multinational	Severe asthma exacerbations Severe exacerbation rate Hospital admissions Reliever/rescue medication use Pneumonia (RTIs)	Funded by AstraZeneca
Rabe 2006a (Rabe et al., 2006)	**Low dose ICS/formoterol maintenance and reliever therapy (MART)** (160/4.5 mcg BUD/FORM, one inhalation twice	2254 people aged ≥12 years with asthma for ≥6 months, using ICS for ≥3 months at a constant dose for ≥4 weeks and using reliever	Severe asthma exacerbations Severe exacerbation rate Asthma control Reliever/medication use	Funded by AstraZeneca Downgraded by one increment due population indirectness – participants could

Study	Intervention and comparison	Population	Outcomes	Comments
	daily plus additional as needed) **Regular low dose ICS/LABA** (160/4.5 mcg BUD/FORM, one inhalation twice daily plus TERB as needed) 12 months	medication on ≥5 of 7 days of the run-in period Exacerbations: yes - >1 in the past year Atopy: not reported International	Hospital admissions Lung function (FEV1 and PEF)	have been receiving any ICS dose prior to study entry (mean ~750 mcg per day)
Renzi 2010 (Renzi et al., 2010)	**Regular low dose ICS/LABA** (50/100 mcg SAL/FP twice daily) **Regular low dose ICS** (100 mcg FP twice daily) 24 weeks	516 people aged ≥12 years receiving SABA alone with a symptom score ≥2 on ≥3 days, disruption of sleep on ≥2 occasions or SABA use on ≥4 days of the last 7 days of the run-in period Exacerbations: not reported Atopy: not reported Canada	Severe asthma exacerbations Severe exacerbation rate Mortality Hospital admissions Reliever/rescue medication use Lung function (FEV1)	Funded by GlaxoSmithKline
Strand 2004 (Strand et al., 2004)	**Regular low dose ICS/LABA** (50/100 mcg SAL/FP twice daily) **Regular low dose ICS** (100 mcg FP twice daily) 24 weeks	150 people aged ≥18 years with GINA defined persistent asthma, using SABA ≥1 time per week Exacerbations: not reported Atopy: not reported Denmark	Severe asthma exacerbations	Funded by GlaxoSmithKline

Table 3: Summary of studies included in the evidence review for further step-up treatment for adults and young people ≥12 years with uncontrolled asthma (review 3.2b).

Study	Intervention and comparison	Population	Outcomes	Comments
Barnes 2007 (Barnes et al., 2007)	**Regular moderate-dose ICS plus montelukast** (800 mcg BUD plus 10 mg MONT per day) **Regular high-dose ICS** (1600 mcg BUD per day) 12 weeks	75 people aged 15-70 with asthma symptoms for >1 year, currently receiving 600-1200 mcg BUD per day with SABA as-needed and symptomatic during the final two weeks of the run-in period whilst receiving 800 mcg BUD per day. Exacerbations: Not reported Atopy: Not reported UK and Canada	Quality of life Lung function (PEF) Adverse events	Funded by Merck, Sharp and Dohme Ltd
Bateman 2004 (Bateman et al., 2004)	**Regular low/moderate/high dose ICS/LABA** (50/100, 50/250 or 50/500 mcg SAL/FP twice per day) **Regular low/moderate/high dose ICS** (100, 250 or 500 mcg FP twice per day) 12 months	2318 people aged 12-80 years with asthma for ≥6 months who did not achieve control of asthma during 4 weeks run-in on their regular ICS therapy (but ER visit of systemic ICS treatment excluded). Mean daily rescue medication use=1.8. Receiving ≤500 mcg (strata 2) or 500-1000 mcg beclomethasone dipropionate equiv (strata 3) at study entry. Exacerbations: Mixed (exacerbation rate between 0.5 to 0.7 in past year) Atopy: Mixed (58 to 63% of participants were atopic) Location not reported	Quality of life Lung function (FEV_1)	Supported by GlaxoSmithKline Indirectness: Intervention (participants had ICS dose up-titrated until asthma control was achieved – could have been low, moderate or high dose)
Bateman 2011 (Bateman et al., 2011)	**Regular low/moderate/high dose ICS plus LAMA** (pre-study ICS: 400-1000 mcg BUD plus 5 mcg TIO once per day)	262 people aged 18-67 years with history of asthma and B16-Arg/Arg genotype & receiving 400-1000 mcg budesonide equivalent per day. Pre-bronchodilator FEV1	Severe asthma exacerbations Quality of life Hospital admissions	Supported by Boehringer Ingelheim and Pfizer Indirectness: Population and intervention –

Study	Intervention and comparison	Population	Outcomes	Comments
	Regular low/moderate/high dose ICS/LABA (pre-study ICS: 400-1000 mcg BUD plus 50 mcg SAL twice daily) 16 weeks	<90% of predicted for those on ICS/LABA, <80% for those on ICS monotherapy Exacerbations: Not reported Atopy: Not reported Multinational	Reliever/rescue medication use Lung function (FEV_1 and PEF) Adverse events Pneumonia	8% of participants had received oral xanthines and/or leukotriene modifiers prior to study entry. Study added LAMA or LABA in to pre-study ICS which could have been low-high dose – protocol specified low-moderate dose ICS plus LAMA vs moderate-high dose ICS/LABA
Bateman 2014 (Bateman et al., 2014)	**Regular moderate dose ICS/LABA** (100/24 mcg FP/VIL once daily) **Regular moderate dose ICS** (100 mcg FF once daily) 24-78 weeks (52 weeks mean)	2019 people aged ≥12 years using ICS at a dose of ≥200 mcg/day FP equiv. or ICS/LABA at a dose of 200/100-500/100 mcg FP/SAL equiv. for ≥12 weeks, and at ≥4 weeks prior to screening and during run-in. Used salbutamol and/or had asthma symptoms on ≥3 out of 7 consecutive days. Exacerbations: Yes (≥ 1 exacerbation in past year was an inclusion criteria) Atopy: not reported International	Severe asthma exacerbations Severe exacerbation rate Mortality Hospital admissions Adverse events	Funded by GlaxoSmithKline
Beasley 2015 (Beasley et al., 2015)	**Regular moderate-dose ICS/LABA** (500/400 mcg IND/MF once daily) **Regular moderate-dose ICS** (400 mcg MF once daily) 21 months	1519 people aged 12-70 years with persistent asthma for ≥6 months (mean ACQ: 1.7) who were treated with or qualified for treatment with an ICS/LABA and had been using an ICS for ≥2 months.	Severe asthma exacerbations Severe exacerbation rate Mortality Asthma control	Sponsored by Novartis Pharma AG

Study	Intervention and comparison	Population	Outcomes	Comments
		Exacerbations: Not reported Atopy: Not reported International	Lung function (FEV_1) Adverse events Pneumonia	
Bernstein 2015 (Bernstein et al., 2015)	**Regular moderate/high dose ICS/LABA** (100/25 or 200/25 mcg FF/VIL once daily **Regular moderate dose ICS** (100 mcg FF once daily) 12 weeks	1039 people >12 years of age with moderate-severe asthma treated with an ICS/LABA for ≥12 weeks. Asthma symptom score ≥3 on the combined day and night asthma symptom scale and/or daily salbutamol use of ≥4 of the last 7 days of the run-in period (during which regular ICS maintained but LABAs removed). Exacerbations: Mixed (29% had exacerbations in last year) Atopy: Not reported Multinational	Severe asthma exacerbations Quality of life Asthma control Lung function (PEF) Adverse events Pneumonia	Funded by GlaxoSmithKline
Bleecker 2014 (Bleecker et al., 2014)	**Regular moderate dose ICS/LABA** (100/25 mcg FF/VIL once daily) **Regular moderate dose ICS** (100 mcg FF once daily) 12 weeks	406 people aged ≥12 years of age receiving a stable low-moderate dose of ICS (100-250 mcg FP twice daily) or a low-dose of ICS/LABA (100/50 mcg FP/SAL twice daily) for ≥4 weeks prior to screening. Mean % rescue-free 24h periods =13.4, 15.3. Exacerbations: not reported Atopy: not reported Multinational	Severe asthma exacerbation Mortality Quality of life Asthma control Reliever/rescue medication use Lung function (FEV1) Pneumonia	Funded by GlaxoSmithKline
Bousquet 2007 (Bousquet et al., 2007)	**Moderate dose ICS/formoterol maintenance and reliever therapy (MART)** (160/4.5 mcg BUD/FORM two inhalations twice	2309 people aged ≥12 years with persistent asthma, treated with ICS alone (800-1600 mcg/day) or ICS/LABA combination (400-1000 mcg/day) for ≥3 months prior to study entry.	Severe asthma exacerbations Mortality Asthma control	Funded by AstraZeneca

Study	Intervention and comparison	Population	Outcomes	Comments
	daily plus additional as-needed) **Regular high dose ICS/LABA** (50/500 mcg SAL/FP one inhalation twice daily) 6 months	Using SABA on ≥5 of 7 days of the run-in (max= 8 inhalations in a single day) Exacerbations: Yes (exacerbation in past year was part of the inclusion criteria) Atopy: not reported International	Hospital admissions Reliever/rescue medication use Lung function (PEF) Adverse events	
Busse 2013 (Busse et al., 2013)	**Regular moderate/high dose ICS/LABA** (100/25 or 200/25 FF/VIL once daily) **Regular high ICS** (500 mcg FP twice daily) 52 weeks	503 people diagnosed with asthma and receiving ICS at a dose of 500-1000 mcg per day with or without additional controller therapy for at least 4 weeks. FEV1 ≥50% of predicted. Exacerbations: Mixed (70% no exacerbation, 20% 1 exacerbation, 10% 2 exacerbations in past 12 months) Atopy: not reported Multinational	Severe asthma exacerbation Mortality Hospital admissions Adverse events Pneumonia	Funded by GlaxoSmithKline
Corren 2013 (Corren et al., 2013)	**Regular moderate dose ICS/LABA** (125/5 mcg FP/FORM, two inhalations twice daily) **Regular moderate dose ICS** (125 mcg FP, two inhalations twice daily) 12 weeks	223 people aged ≥12 years with asthma diagnosis for ≥12 months and receiving ICS therapy for ≥4 weeks prior to screening at a dose ≤500 mcg per day fluticasone equiv. ≥2 SABA inhalations on ≥3 out of 7 consecutive days of the 2-week run-in as well as symptoms on ≥3 days or 1 night Exacerbations: not reported Atopy: not reported International	Severe asthma exacerbation Mortality Rescue/reliever medication use Lung function (FEV1 % pred and PEF) Adverse events	Sponsored by SkyePharma
Emami 2014 (Emami et al., 2014)	**Regular moderate dose ICS/LABA** (160/4.5 mcg BUD/FORM, two	51 people aged 18-65 years with moderate asthma (symptoms begin with light exercise, 1-2 asthma attacks per	Asthma control Lung function (FEV1 % predicted)	

Study	Intervention and comparison	Population	Outcomes	Comments
	inhalations twice daily) Regular moderate dose ICS (180 mcg BUD, two inhalations twice daily) 12 weeks	week, and FEV1 60%-80%) or severe asthma (severe limitations in performing activities, >2 asthma attacks per week, and FEV1 <60%) Exacerbations: not reported Atopy: not reported Iran		
Fish 2001 (Fish et al., 2001)	**Regular low/moderate/high dose ICS/LABA** (pre-study ICS plus 50 mcg SAL twice daily) **Regular low/moderate/high dose ICS plus montelukast** (pre-study ICS plus 10 mg MONT once daily) 12 weeks	948 people aged ≥15 years with asthma for ≥6 months & symptomatic despite receiving ICS for ≥6 weeks and at a constant dose for ≥30 days. Mean of ≥4 SABA uses per day, symptom score ≥2 on ≥3 days and awakening due to asthma on ≥3 days on the 7 days prior to randomisation. Exacerbations: not reported Atopy: not reported USA and Puerto Rico	Severe asthma exacerbation Rescue/reliever medication use Pneumonia	Funded by Glaxo Wellcome. Intervention indirectness - participants were kept on their usual ICS regimen, which could have been low, moderate or high dose, in addition to study drugs
Hoshino 2019 (Hoshino et al., 2019)	**Regular low dose ICS/LABA + montelukast** (160/4.5 mcg BUD/FORM, two inhalations once daily plus 10 mg MONT once daily) **Regular low dose ICS/LABA + LAMA** (160/4.5 mcg BUD/FORM, two inhalations once daily plus 5 mcg TIO once daily) 48 weeks	57 people with asthma ≥3 months and symptomatic (AQLQ score, symptom domain = 5.6; 5.5) at screening. Receiving ICS plus LABA for ≥4 weeks prior to screening. Exacerbations: Mixed (majority not exacerbating in the past year; montelukast 34%, LAMA 36%) Atopy: Mixed (majority atopic; Montelukast n=18/28, LAMA n=20/29.) Location not reported	Severe asthma exacerbation Quality of life Lung function (FEV1 % predicted) Inflammatory markers (FeNO)	
Huchon 2009	**Regular moderate-high-dose ICS/LABA** (100/6	645 people aged 18-70 years with moderate-severe persistent	Severe asthma exacerbations	Funded by Chiesi

Study	Intervention and comparison	Population	Outcomes	Comments
(Huchon et al., 2009)	extra fine BDP/FORM or 250 mcg BDP plus 6 mcg FORM, both taken as two inhalations twice per day) **Regular high-dose ICS** (250 mcg BDP, two inhalations twice per day) 24 weeks	asthma, receiving 750-1000 mcg BDP per day with or without a LABA, with symptoms >3 times during the previous week Exacerbations: Not reported Atopy: Not reported International	Lung function (FEV_1 and PEF)	Farmaceutici SpA
Ind 2003 (Ind et al., 2003)	**Regular moderate dose ICS/LABA** (50/250 mcg FP/SAL, one inhalation twice daily) **Regular moderate/high dose ICS** (250 or 500 mcg FP, one inhalation twice daily) 24 weeks	496 people aged 16-75 years and symptomatic with asthma whilst receiving 500-800 mcg beclomethasone twice daily. Exacerbations: yes (at least two exacerbations leading to a change in therapy or hospitalisation in the past year, with at least one in the past 6 months) Atopy: not reported. Multinational	Severe asthma exacerbations	Funded by GlaxoWellcome Population indirectness - 2% receiving anti-allergics, 6% receiving anticholinergics, 10% receiving xanthines
Jenkins 2000 (Jenkins et al., 2000)	**Regular moderate dose** ICS/LABA (50/250 mcg SAL/FP twice daily) **Regular high dose ICS** (800 mcg BUD twice daily) 24 weeks	353 people aged ≥12 years and receiving 800-1200 mcg/day of beclomethasone or budesonide or 400-600 mcg/day fluticasone propionate for ≥4 weeks. SABA use more than twice daily, or had a total daily symptom score ≥2 on ≥4 out of 7 days of run-in. Exacerbations: Mixed (acute exacerbation requiring hospitalisation within 4 weeks an exclusion criteria). No further information. Atopy: not reported International	Severe asthma exacerbation Lung function (PEF and FEV1)) Pneumonia	Funded by Glaxo Wellcome

Study	Intervention and comparison	Population	Outcomes	Comments
Juniper 2002 (Juniper et al., 2002)	**Regular moderate dose ICS/LABA** (50/250 mcg SAL/FP twice daily) **Regular high dose ICS** (800 mcg BUD twice daily) 12 weeks	113 people aged ≥12 years receiving inhaled beclomethasone or budesonide at a dose of 800-1200 mcg per day or fluticasone propionate at a dose of 400-600 mcg per day for at least 4 weeks. Mean FEV1 % pred=68; 72 Exacerbations: mixed (exacerbation within last 4 weeks an exclusion criteria, but no other information reported) Atopy: not reported Multinational	Quality of life	Sponsored by GlaxoSmithKline
Katial 2011 (Katial et al., 2011)	**Regular moderate dose ICS/LABA** 50/250 mcg SAL/FP twice daily) **Regular moderate dose ICS** (250 mcg FP twice daily) 52 weeks	621 people aged ≥12 years symptomatic whilst treated with low-moderate dose of ICS or ICS/LABA for ≥4 weeks prior to screening. Asthma symptom score ≥1 on ≥2 days and SABA use on any 2 or more days during any single week of the run-in. Exacerbations: not reported Atopy: mixed [majority atopic: ICS/LABA n= 181 (60%), ICS n= 194 (62%)] International	Severe asthma exacerbations Reliever/rescue medication use Lung function (FEV1 % pred and PEF)	Funded by GlaxoSmithKline
Kerstjens 2015 (Kerstjens et al., 2015)	**Regular moderate dose ICS/LABA** (pre-study ICS plus 50 mcg SAL twice daily) **Regular moderate dose ICS + LAMA** (pre-study ICS plus 2.5 or 5 mcg TIO once daily) 24 weeks	1580 people aged 18-75 years, diagnosed with asthma before age of 40 years and symptomatic (ACQ score>1.5). Receiving stable moderate-dose ICS (400-800 mcg budesonide equivalent) alone or in combination with LABA/SABA for at least 4 weeks.	Severe asthma exacerbation Adverse events Pneumonia	Funded by Boehringer Ingelheim. Population indirectness - 9% of participants were treated with leukotriene modifiers at screening

Study	Intervention and comparison	Population	Outcomes	Comments
		Exacerbations: not reported Atopy: not reported Multinational		
Kerstjens 2020 (Kerstjens et al., 2020)	**Regular low dose ICS/LABA + LAMA** (80/150/50 or 160/150/50 MF/IND/GLY once per day) **Regular moderate/high dose ICS/LABA** (320/150 MF/IND once daily or 500/50 FP/SAL twice daily 52 weeks	2475 people aged 18-75 years symptomatic during run-in (ACQ score >1.5) and history of at least one exacerbation that required medical attention and systemic corticosteroids in the past year. Receiving moderate-high dose ICS/LABA for at least 3 months, and at a stable dose for a month. Exacerbations: Yes - all had at least one within the year Atopy: not reported Multinational	Severe asthma exacerbation Mortality Quality of life Reliever/rescue medication use Adverse events Pneumonia	Funded by Novaritis
Kerwin 2011 (Kerwin et al., 2011)	**Regular moderate dose ICS/LABA** (250/50 mcg FP/SAL twice daily) **Regular moderate dose ICS** (250 mcg FP twice daily) 52 weeks	628 people aged ≥12 years receiving moderate-low dose ICS or low-dose ICS/LABA combination for ≥4 weeks prior to screening. Asthma symptom score ≥1 on ≥2 days and SABA use on ≥2 days during 2/3 week run-in. Exacerbations: not reported Atopy: not reported International	Severe asthma exacerbation Mortality Asthma control Rescue/reliever medication use Lung function (PEF and FEV1 % predicted) Adverse events	Funded by GlaxoSmithKline
Kuna 2007 (Kuna et al., 2007)	**Low dose ICS/formoterol maintenance and reliever therapy (MART)** (160/4.5 mcg BUD/FORM, one inhalation twice daily plus additional as needed)	3335 people aged ≥12 years using ICS for ≥3 months and at a dose of ≥500 mcg/day (BUD or FP) or ≥1000 mcg/day (any other ICS) for ≥1 month. Using reliever medication on ≥5 days out of the last 7 during a 2-week run-in.	Severe asthma exacerbation Mortality Hospital admissions	Funded by AstraZeneca

Study	Intervention and comparison	Population	Outcomes	Comments
	Regular moderate dose ICS/LABA (25/125 mcg SAL/FP, two inhalations twice daily or 320/9 mcg BUD/FORM, one inhalation twice daily) 24 weeks	Exacerbations: yes, all participants had at least one exacerbation in the past year Atopy: not reported Location not reported		
Lee 2020 (Lee et al., 2020)	**Regular moderate dose ICS/LABA + LAMA** (100/31.25/25 or 100/62.5/25 mcg FF/UMEC/VIL once daily) **Regular moderate/high dose ICS/LABA** (100/25 or 200/25 mcg FF/VIL once daily) 52 weeks	1624 people aged ≥18 years with inadequately controlled asthma symptoms (ACQ score ≥1.5, documented healthcare contact or acute change in asthma therapy within a year). Receiving ICS/LABA for ≥12 weeks with no changes in dose for ≥6 weeks prior to screening. Exacerbations: mixed (in past 12 months: 0=37%, 1=48%, ≥2=16%) Atopy: not reported Location not reported	Mortality Adverse events	Funded by GlaxoSmithKline
Lin 2015 (Lin et al., 2015)	Regular high dose ICS/LABA (200/25 mcg FF/VIL once daily) Vs Regular high dose ICS (500 mcg FP twice daily) 12 weeks	309 people aged ≥ 12 years receiving ICS or ICS/LABA for ≥12 weeks and at a stable strength for ≥4 weeks (500 mcg FP or 250/50 FP/SAL). FEV1 40-90% of predicted. Exacerbations: Mixed (Exacerbation requiring oral corticosteroids within 12 weeks was an exclusion criterion, no further information reported.) Atopy: not reported Multinational	Severe asthma exacerbation Mortality Quality of life Asthma control Reliever/rescue medication use Lung function (PEF) Adverse events Pneumonia	Funded by GlaxoSmithKline
Lin 2019 (Lin et al., 2019)	**Regular moderate dose ICS/LABA** (pre-study ICS plus 50 mcg SAL twice daily)	325 people aged 18 to 75 years on maintenance treatment with stable moderate-dose ICS (400–800 µg	Mortality Hospital admissions Lung function (FEV1)	Secondary publication of Kerstjens 2015

Study	Intervention and comparison	Population	Outcomes	Comments
	Regular moderate dose ICS + LAMA (pre-study ICS plus 2.5 or 5 mcg TIO once daily) 24 weeks	budesonide or equiv.) (alone or in a fixed combination with a LABA or SABA) for at least 4 weeks. Symptomatic at screening with a mean ACQ score of ≥1.5. Exacerbations: not reported. Atopy: not reported. China		
Mitchell 2003 (Mitchell et al., 2003)	**Regular high dose ICS/LABA** (250 mcg BDP, two inhalations twice per day plus 12 mcg FORM twice daily) **Regular high dose ICS** (250 mcg BDP, four inhalations twice daily) 12 weeks	203 people aged ≥18 years with moderate-severe asthma. Waking ≥1 time per night due to asthma, asthma interfering with daily activities ≥1 time per day, using SABA ≥4 times per day or diurnal PEFv >15% on ≥2 days out of the last 7 of the run-in period. Receiving ICS at a dose of 1000 mcg beclomethasone, or 800 mcg budesonide for at least one month before screening. Exacerbations: not reported. Atopy: not reported Australia	Severe asthma exacerbations Reliever/rescue medication use Lung function (PEF) Adverse events Adrenal insufficiency	Sponsored by Novartis Pharmaceutical Australia Pty Ltd
Nabil 2014 (Nabil et al., 2014)	**Regular moderate dose ICS/LABA** (400/12 mcg BUD/FORM twice daily) Regular high dose ICS (800 mcg BUD twice daily) 6 months Egypt	60 people aged ≥18 years with moderate-severe persistent asthma. Uncontrolled on low dose ICS (budesonide or beclomethasone at 400 mcg per day) Exacerbations: not reported. Atopy: not reported	Lung function (FEV1 % predicted)	Population indirectness - no description of what defined uncontrolled asthma
Noonan 2006 (Noonan et al., 2006)	**Regular moderate dose ICS/LABA** (160/4.5 mcg BUD/FORM, two	348 people aged ≥12 years receiving moderate/high dose ICS, either alone or in combination with other	Severe asthma exacerbation	Funded by AstraZeneca

Study	Intervention and comparison	Population	Outcomes	Comments
	inhalations twice daily) **Regular moderate dose ICS** (160 mcg BUD, two inhalations twice daily) 12 weeks	asthma maintenance medications consistently for ≥4 weeks Exacerbations: Mixed (hospitalisation or emergency treatment for asthma ≥1 time in the past 6 months was an exclusion criteria. No further information reported) Atopy: not reported USA		
O'Byrne 2005 (O'Byrne et al., 2005)	**Low dose ICS/formoterol maintenance and reliever therapy (MART)** (80/4.5 mcg BUD/FORM twice daily plus additional as needed) **Regular moderate dose ICS** (320 mcg BUD twice daily)12 months	1851 people aged 4-80 years treated with 400-1000 mcg (adults) or 200-500 mcg (children 4-11 years) per day at a constant dose for ≥3 months. ≥12 inhalations (≥8 for children) of as-needed medication during the last 10 days of the run-in. Exacerbations: Yes - inclusion criteria was at least one exacerbation in the past year. Atopy: not reported Multinational	Severe asthma exacerbations Reliever/rescue medication use (day and night time) Lung function (FEV1 and PEF) Adverse events Pneumonia	Supported by AstraZeneca Population indirectness - included both adults and children (12%)
O'Byrne 2014 (O'Byrne et al., 2014)	**Regular high dose ICS/LABA** (200/25 mcg FF/VIL once daily) **Regular high dose ICS** (500 mcg FP twice daily or 200 mcg FF once daily) 24 weeks	586 people aged ≥12 years with asthma symptoms equating to a score ≥3 on the asthma symptom scale and/or daily SABA use on ≥4 of the final 7 days of the run-in. Using ICS, with or without LABA, for ≥12 weeks with stable ICS dose (FP 500 mg twice daily (or equivalent) or mid-dose ICS/LABA (FP/salmeterol 250/50 mg twice daily or equivalent)) for ≥4 weeks Exacerbations: Mixed (exacerbation requiring overnight hospitalisation	Severe asthma exacerbation Mortality Quality of life Asthma control Reliever/rescue medication use Lung function (FEV1 and PEF) Adverse events Pneumonia	Funded by GlaxoSmithKline

Study	Intervention and comparison	Population	Outcomes	Comments
		or emergency department attendance within 6 months of screening, or requiring oral corticosteroids within 12 weeks of screening were a exclusion criteria. No further information reported) Atopy: not reported International		
Paggiaro 2016 (Paggiaro et al., 2016)	**Regular moderate dose ICS/LABA** (200/6 mcg BDP/FORM, two inhalations twice daily) **Regular moderate dose ICS** (100 mcg BDP, four inhalations twice daily) 12 weeks	376 people aged ≥18 years with partly or not controlled asthma, based on GINA asthma control parameters, and an asthma control questionnaire >0.75. Receiving high dose ICS monotherapy (BDP non-extrafine >1000 µg/day, or equivalent) or moderate dose of ICS (BDP non-extrafine 500–1000 µg/day or equivalent) in combination with LABA Exacerbations: not reported Atopy: not reported International	Severe asthma exacerbation Lung function (PEF) Adverse events Adrenal insufficiency	Supported by Chiesi Farmaceutici
Patel 2013 (Patel et al., 2013)	**Moderate dose ICS/formoterol maintenance and reliever therapy (MART)** (200/6 mcg BUD/FORM, two inhalations twice daily plus additional as needed) **Regular moderate dose ICS/LABA** (200/6 mcg BUD/FORM, two inhalations twice daily) 24 weeks	303 people aged 16-65 years receiving ICS (mean ACQ-7 score = 1.87, 1.90) Exacerbations: Yes, at least one exacerbation requiring a GP/ER visit resulting in oral corticosteroid prescription in the past year Atopy: not reported New Zealand	Severe asthma exacerbations Mortality Asthma control Hospital admissions Rescue/Reliever mediation use Lung function (FEV1)	Population indirectness - 15% of participants did not have asthma that was uncontrolled

Study	Intervention and comparison	Population	Outcomes	Comments
Pavord 2009 (Pavord et al., 2009)	**Low dose ICS/formoterol maintenance and reliever therapy (MART)** (200/6 mcg BUD/FORM, one inhalation twice daily plus additional as needed) **Regular high dose ICS/LABA** (400/12 mcg BUD/FORM plus 400 mcg BUD, one inhalation of each twice per day) 12 months	127 people aged 18-65 years receiving ICS at a dose of 400-1000 mcg in combination with a LABA, or 800-1600 as monotherapy. Used SABA or reported symptoms on ≥4 of the last 7 days of the run-in period. Exacerbations: not reported Atopy: not reported Multinational	Mortality Reliever/rescue medication use	Supported by AstraZeneca
Pertseva 2013 (Pertseva et al., 2013)	Regular moderate dose ICS/LABA (250/10 mcg FP/FORM twice daily) Regular moderate dose ICS (250 mcg FP twice daily) 12 weeks	438 people aged ≥12 years receiving ICS at a dose of ≤500 mcg fluticasone equiv. for ≥4 weeks and be considered suitable for ICS/LABA therapy. ≥2 inhalations of SABA on ≥3 out of 7 days and ≥1 night with sleep disturbance or ≥3 days with asthma symptoms during run-in. Exacerbations: not reported Atopy: not reported International	Severe asthma exacerbation Mortality Reliever/rescue medication use Lung function (FEV1) Adverse events	Funded by Skyepharma and Abbott Respiratory LLC
Peters 2008 (Peters et al., 2008)	Regular moderate /high ICS/LABA (160/4.5 mcg BUD/FORM, two or four inhalations twice daily) Regular high dose ICS (160 mcg BUD, four inhalations twice daily) 52 weeks	706 people aged ≥12 years receiving moderate/high dose ICS, or low-high dose ICS/LABA consistently for ≥4 weeks before screening. ≥2 controller medication uses, ≥2 nighttime awakenings due to asthma or ≥3 rescue medication uses in the previous week. Exacerbations: not reported Atopy: not reported Location not reported	Severe asthma exacerbation Mortality Rescue/reliever medication use Lung function (FEV1 and PEF) Adverse events Pneumonia	Funded by AstraZeneca

Study	Intervention and comparison	Population	Outcomes	Comments
Price 2003 (Price et al., 2003)	**Regular moderate-dose ICS plus montelukast** (800 mcg BUD plus 10 mg MONT per day) **Regular high-dose ICS** (1600 mcg BUD per day) 12 weeks	889 people aged 15-75 years with asthma not optimally controlled whilst receiving 600-1200 mcg BUD per day with symptoms requiring SABA use at least once daily during the final two weeks of the run-in period. Exacerbations: 41.4% exacerbated in the past year Atopy: Not reported Location not reported	Severe asthma exacerbations Lung function (PEF) Adverse events	Supported by Merck and Co Inc
Price 2011 (Price et al., 2011)	**Regular low/moderate dose ICS plus montelukast** (10 mg MONT or 20 mg ZAF per day plus pre-study ICS (dose changeable as needed throughout the study) **Regular low/moderate dose ICS/LABA** (SAL or FORM, dose not specified) plus pre-study ICS (dose changeable as needed throughout the study) 2 years	352 people aged 12-80 years receiving ICS for ≥12 weeks. Score ≥1-6 on the ACQ Exacerbations: mixed - average 0.18 and 0.24 in past year in ICS + montelukast and ICS/LABA arms, respectively Atopy: not reported UK	Mortality Quality of life Asthma control Hospital admissions Reliever/rescue medication use Lung function (PEF)	Funded by NIHR Intervention indirectness - could have been treated with either montelukast or zafirlukast, protocol specified montelukast, and flexible dosing of ICS throughout the study
Scicchitano 2004 (Scicchitano et al., 2004)	**Low dose ICS/Formoterol maintenance and reliever therapy (MART)** (160/4.5 mcg BUD/FORM, two inhalations once daily plus additional as needed) **Regular moderate dose ICS** (160 mcg BUD, two inhalations twice daily) 12 months	1890 people aged 12-80 years symptomatic with moderate-severe asthma (according to medication needs) during run-in. Mean SABA uses per day = 1.9, 2.0. Receiving ICS at a dose of 400-1600 mcg per day for ≥3 months and at a constant dose for ≥30 days pre-study. Exacerbations: yes - exacerbation within	Severe asthma exacerbation Mortality Rescue/reliever medication use Lung function (PEF) Adverse events	Supported by AstraZeneca

Study	Intervention and comparison	Population	Outcomes	Comments
		past-year was an inclusion criteria Atopy: not reported Multinational		
Shapiro 2000 (Shapiro et al., 2000)	**Regular moderate dose ICS/LABA** (250/50 mcg FP/SAL twice daily) **Regular moderate dose ICS** (250 mcg FP twice daily) 12 weeks	168 people ≥12 years who received ICS continuously for at least 12 weeks and at a constant dose for at least 4 weeks (beclomethasone dipropionate (462-672 mcg/d), triamcinolone acetonide (1,100-1,600 mcg/d), flunisolide (1,250-2,000 mcg/d), fluticasone propionate (440 mcg/d). FEV1 40-85% of predicted Exacerbations: not reported Atopy: not reported USA	Reliever/rescue medication use Lung function (FEV1 and PEF) Adrenal insufficiency	Supported by Glaxo Wellcome
Sher 2017 (Sher et al., 2017)	**Regular moderate dose ICS** (200 mcg FP twice daily) **Regular moderate dose ICS/LABA** (200/25 mcg FP/SAL twice daily) 12 weeks Multinational	292 people aged ≥12 years with persistent asthma (symptoms or reliever medication use >2 days per week or night awakenings >3 times a month). Receiving ICS, with or without a LABA, at a dose >200 mcg fluticasone propionate per day for ≥1 month Exacerbations: mixed (exacerbation requiring systemic corticosteroids within 30 days or hospitalisation for asthma within 2 months were exclusion criteria. No further information.) Atopy: not reported	Mortality Quality of life Reliever/rescue medication use Lung function (FEV1 and PEF) Adverse events Pneumonia	Sponsored by Teva Branded Pharmaceuticals R&D
Spector 2012 (Spector et al., 2012)	Regular moderate dose ICS/LABA (160/4.5 mcg BUD/FORM, two	311 people aged ≥12 years and black ethnicity. Receiving ICS at a moderate-high dose for ≥30 days prior to	Mortality Reliever/rescue medication use	Supported by AstraZeneca

Study	Intervention and comparison	Population	Outcomes	Comments
	inhalations twice daily) Regular moderate dose ICS (180 mcg BUD, two inhalations twice daily) 12 weeks	screening and symptomatic (daytime or nighttime symptom scores >0 on ≥3 out of 7 consecutive days) during 2-week run-in period. Exacerbations: not reported Atopy: not reported USA	Lung function (FEV1 and PEF) Adverse events	
Stirbulov 2012 (Stirbulov et al., 2012)	**Regular moderate dose ICS/LABA** (400/12 mcg BUD/FORM twice daily) **Regular moderate dose ICS** (400 mcg BUD twice daily) 12 weeks	People with partially controlled persistent asthma, as determined based on the classifications proposed by the Global Strategy for Asthma Management and Prevention and the Fourth Brazilian Guidelines for Asthma Management Exacerbations: not reported Atopy: not reported Brazil	Reliever/rescue medication use Lung function (FEV1 and PEF)	Population indirectness as initially therapy of the participants while they were uncontrolled was not specified
Takeyama 2014 (Takeyama et al., 2014)	**Moderate dose ICS/formoterol maintenance and reliever therapy (MART)** (160/4.5 mcg BUD/FORM, two inhalations twice daily plus additional as needed) **Regular moderate dose ICS/LABA inhaler** (160/4.5 mcg BUD/FORM, two inhalations twice daily) 48 weeks	63 people aged 16-80 years with Asthma Control Test score ≤20 and reliever medication use ≥5 times a week. Treated with constant dose of ICS (budesonide 320-640 mcg/day, fluticasone 200-500 mcg/day) plus LABA for ≥3 months Exacerbations: yes - inclusion criteria specified ≥1 in past year Atopy: not reported Location not reported	Severe asthma exacerbation Reliever/rescue medication use	
van Zyl-Smit 2020 (van Zyl-Smit et al., 2020)	**Regular high dose ICS** (400 mcg MF twice daily) **Regular moderate/high dose**	1333 people aged 12-75 years with ACQ-7 score of at least 1·5 at screening. Receiving moderate-dose or high-dose ICS monotherapy	Mortality Adverse events Pneumonia	Funded by Novartis

Study	Intervention and comparison	Population	Outcomes	Comments
	ICS/LABA (500/50 mcg FP/SAL twice daily or 320/150 MF/IND once daily) 52 weeks	or low-dose ICS–LABA combination for asthma for at least 3 months and at stable doses for at least 1 month before screening. Exacerbations: mixed - 69% none, 24% one, 7% more than one in the past year Atopy: not reported Multinational		
Virchow 2019 (Virchow et al., 2019)	**Regular moderate dose ICS/LABA plus LAMA** (100/6/10 mcg BDP/FORM/GLY, two inhalations twice daily) **Regular moderate dose ICS/LABA** (100/6 mcg BDP/FORM, two inhalations twice daily) 52 weeks	1155 people aged 18-75 years with ACQ score ≥1.5 and receiving a stable moderate-dose of ICS plus a LABA for ≥4 weeks prior to screening Exacerbations: yes - ≥1 exacerbation requiring systemic corticosteroids, emergency department visit or hospitalisation in the past year was an inclusion criteria. Atopy: not reported International	Severe asthma exacerbation Mortality Lung function (FEV1 and PEF) Adverse events Pneumonia	Funded by Chiesi Farmaceutici
Vogelmeier 2005 (Vogelmeier et al., 2005)	**Moderate dose ICS/formoterol maintenance and reliever therapy (MART)** (160/4.5 mcg BUD/FORM, two inhalations twice daily plus additional as needed) **Regular moderate dose ICS/LABA** (50/250 mcg SAL/FP twice daily) 52 weeks	2143 people aged ≥12 years receiving ≥500 mcg budesonide, fluticasone, or ≥1000 mcg of any other ICS per day for at least once month prior to the study. Used as-needed medication on ≥4 of the last 7 days of the run-in. Exacerbations: yes - all participants had at least one exacerbation in the past year Atopy: not reported Multinational	Severe asthma exacerbations Mortality Quality of life Asthma control Rescue/reliever medication use Lung function (FEV1) Adverse events	Supported by AstraZeneca Intervention indirectness due to the down-titration of ICS/LABA from moderate to low-dose, where deemed appropriate
Wallin 2003 (Wallin et al., 2003)	**Regular high dose ICS** (500 mcg FP twice daily)	37 people with need for extension of treatment on the basis of both symptoms (≥6 days, ≥4 nights with symptoms or	Severe asthma exacerbation	Supported by Glaxo Wellcome

Study	Intervention and comparison	Population	Outcomes	Comments
	Regular moderate dose ICS/LABA (200/50 mcg FP/SAL twice daily) 12 weeks	SABA use) and pulmonary function during the last 2 weeks of the run-in. At entry receiving 800-1200 mcg budesonide or 400-500 mcg fluticasone propionate per day Exacerbations: not reported. Atopy: mixed - 22/37 participants with positive skin prick test Norway		
Wang 2015 (Wang et al., 2015)	**Regular moderate dose ICS/LABA plus LAMA** (50/250 mcg SAL/FP twice daily plus 18 mcg TIO once daily) **Regular moderate dose ICS/LABA plus montelukast** (50/250 mcg SAL/FP twice daily plus 10 mg MONT once daily) **Regular moderate dose ICS/LABA** (50/500 mcg SAL/FP twice daily) 12 weeks	94 people with moderate asthma and daily symptoms, daily use of SABA. ACT score 12-20. Exacerbations: not reported Atopy: not reported China	Asthma control Inflammatory markers (FeNo)	
Ye 2015 (Ye et al., 2015)	**Regular low dose ICS plus montelukast** (400 mcg BUD plus 10 mg MONT daily) **Regular moderate dose ICS** (800 mcg BUD per day) 12 months	140 people aged 60-75 years being treated with ICS (budesonide 400 µg/day or equivalent) or a combination of low dose inhaled budesonide and LABA (Seretide 250 µg/day or equivalent) for over 1 month before participating in this study. Did not meet criteria of GINA-defined 'well controlled asthma' (symptoms, use of reliever and lung function) after 4-week run-in period.	Severe asthma exacerbation Asthma control Lung function (FEV1 % pred)	

Study	Intervention and comparison	Population	Outcomes	Comments
		Korea		
Zangrilli 2011 (Zangrilli et al., 2011)	**Regular moderate dose ICS/LABA** (160/4.5 mcg BUD/FORM, two inhalations twice daily) **Regular moderate dose ICS** (160 mcg BUD, two inhalations twice daily) 12 weeks	250 Hispanic people aged ≥12 years receiving moderate-high dose ICS alone or in combination with a LABA for ≥30 days. Day or nighttime symptom scores >0 on ≥3 of 7 consecutive days during the run-in period. Exacerbations: not reported Atopy: not reported USA	Mortality Reliever/rescue medication use Adverse events	Funded by AstraZeneca
Zetterstrom 2001 (Zetterstrom et al., 2001)	Regular moderate dose ICS/LABA (160/4.5 mcg BUD/FORM or 200 mcg BUD plus 4.5 mcg FORM, two inhalations twice daily) Regular moderate dose ICS (200 mcg BUD, two inhalations twice daily) 12 weeks	362 people aged ≥18 years receiving ICS at a constant daily dose ≥500 mcg for ≥30 days. FEV1 50-90% of predicted. Exacerbations: not reported Atopy: not reported Multinational	Severe asthma exacerbation Reliever/rescue medication use Lung function (PEF and FEV1) Pneumonia	Funded by AstraZeneca

Children aged 5-11 years

Table 4: Summary of studies included in the evidence review for children aged 5-11 years

Study	Intervention and comparison	Population	Outcomes	Comments
Berger 2010 (Berger et al., 2010)	**Regular paediatric high dose ICS/LABA** (160/4.5 mcg BUD/FORM, two inhalations twice daily) **Regular paediatric high dose ICS** (200 mcg BUD, two inhalations twice daily)	187 children aged 6-11 years receiving ICS, either alone or in addition to other controller medication Exacerbations: mixed (treatment requiring systemic corticosteroids within 4 weeks	Quality of life Hospital admissions (urgent care visits) Adverse events Pneumonia	Funded by AstraZeneca

Study	Intervention and comparison	Population	Outcomes	Comments
	26 weeks	before screening or during run-in was an exclusion criteria. Atopy: not reported USA		
Bisgaard 2006 (Bisgaard et al., 2006)	**Regular paediatric moderate dose ICS** (320 mcg BUD once daily) **Regular paediatric low dose ICS/LABA** (80/4.5 mcg BUD/FORM once daily) **Paediatric low dose ICS/formoterol maintenance and reliever therapy (MART)** (80/4.5 mcg BUD/FORM once daily plus additional inhalations as-needed) 12 months	341 children aged 4-11 years receiving 200-500 mcg ICS per day with ≥8 SABA uses in the last 10 days of the run-in period Exacerbations: Yes – inclusion criteria was at least one in past 12 months Atopy: not reported Multinational	Severe asthma exacerbations Severe exacerbation rate Reliever/rescue medication use Adverse events Adrenal insufficiency (morning cortisol <400 nmol/L) Pneumonia	Funded by AstraZeneca
de Blic 2009 (de Blic et al., 2009)	**Regular paediatric moderate dose ICS/LABA** (100/50 mcg FP/SAL twice daily) **Regular paediatric high dose ICS** (100 mcg FP, two inhalations twice daily) 12 weeks	321 children aged 4-11 years receiving 400 mcg BDP (beclomethasone dipropionate) per day with asthma that was not controlled on ≥2 of 4 weeks of the run-in period whilst receiving 100 mcg FP (fluticasone propionate) Exacerbations: not reported Atopy: 84% atopic in ICS/LABA arm, 91% in ICS arm Europe	Severe asthma exacerbations Reliever/rescue medication use Lung function (PEF) Adverse events	Funded by GlaxoSmithKline

Study	Intervention and comparison	Population	Outcomes	Comments
Lenney 2013 (Lenney et al., 2013)	**Regular paediatric moderate dose ICS** (100 mcg FP twice daily) **Regular paediatric moderate ICS/LABA** (100/50 mcg FP/SAL twice daily) **Regular paediatric moderate dose ICS with montelukast** (100 mcg FP twice daily plus 5 mg montelukast once daily) 48 weeks	63 children aged 6-11 years who used ≥7 SABA inhalations in the past 7 days and had asthma symptoms Exacerbations: mixed (patients included who have had exacerbations (defined as a short course of oral corticosteroids, and unscheduled GP or A&E Department visit or a hospital admission within the previous 6 months) Atopy: not reported UK	Severe asthma exacerbations Quality of life Hospital admissions Lung function (FEV1 % pred) Adverse events	Funded by NIHR Closed early due to inadequate recruitment Downgraded by one increment due to population indirectness – includes adolescents as well as children
Malone 2005 (Malone et al., 2005)	**Regular paediatric moderate dose ICS/LABA** (100/50 mcg FP/SAL twice daily) **Regular paediatric moderate dose ICS** (100 mcg FP twice daily) 12 weeks	203 children aged 4-11 years receiving ICS with daytime symptoms and/or SABA use on ≥3 of 7 days on the run-in period Exacerbations: No. History of life-threatening asthma; hospitalization due to asthma twice or more in the previous year were exclusion criteria. Patients were required not to have used oral or parenteral corticosteroids for at least 1 month before screening. Atopy: Not reported	Severe asthma exacerbations Adverse events Pneumonia	Funded by GlaxoSmithKline

Study	Intervention and comparison	Population	Outcomes	Comments
		USA and Canada		
Morice 2008 (Morice et al., 2008)	**Regular paediatric moderate dose ICS/LABA** (80/4.5 mcg BUD/FORM via DPI or pMDI (two study arms combined for this review), two inhalations twice daily) **Regular paediatric moderate dose ICS** (100 mcg BUD, two inhalations twice daily) 12 weeks	622 children aged 6-11 years currently receiving regular ICS with symptoms on ≥4 of the last 7 days of the run-in period and a morning PEF <85% of predicted Exacerbations: Not reported Atopy: Not reported Multinational	Quality of life Adverse events	Funded by AstraZeneca
Pearlman 2017 (Pearlman et al., 2017)	**Regular paediatric moderate dose ICS/LABA** (80/4.5 or 80/2.25 mcg BUD/FORM, two inhalations twice daily) **Regular paediatric moderate dose ICS** (80 mcg BUD, two inhalations twice daily) 12 weeks	279 children aged 6-12 years currently receiving moderate-dose ICS or ICS/LABA, and with asthma symptoms or use of rescue medication on at least 4 of 7 consecutive days prior to randomisation Exacerbations: Mixed (hospitalization or emergency treatment for asthma within 6 months before enrolment was an exclusion criteria). Atopy: Not reported USA, Mexico, Panama and Slovakia	Severe asthma exacerbations Mortality Reliever/rescue medication use Lung function (PEF) Adverse events	Funded by Astrazeneca
Vaessen-Verberne 2010 (Vaessen-Verberne et al., 2010)	**Regular paediatric moderate dose ICS/LABA** (50/100 mcg SAL/FP twice daily)	158 children aged 6-16 years receiving <250 mcg ICS per day with symptoms during the 2-week run-in period	Severe asthma exacerbations (requiring hospitalisation or oral steroids)	Funded by GlaxoSmithKline

Study	Intervention and comparison	Population	Outcomes	Comments
	Regular paediatric high dose ICS (200 mcg FP twice daily) 26 weeks	Exacerbations: mixed – 70% had none in the past year Atopy: mixed – 60% atopic The Netherlands	Lung function (FEV1 % pred and PEF % pred) Adverse events	

Children under 5 years

Table 5: Summary of studies included in the evidence review for children under 5 years

Study	Intervention and comparison	Population	Outcomes	Comments
Fitzpatrick 2016 (Fitzpatrick et al., 2016)	**Regular ICS** (44 mcg FP, two inhalations twice daily) **As-needed ICS/SABA** (44 mcg FP plus 90 mcg salbutamol, two inhalations as-needed) **Regular montelukast** (4 mg montelukast once daily) 48 weeks	230 infants aged 12-59 months who met the criteria for requiring step-2 treatment, currently receiving intermittent bronchodilators, low-dose ICS or LTRAs with symptoms ≥2 days per week over the past month Exacerbations: mixed – 75% with an exacerbation in the past year Atopy: mixed – 44% positive to one aeroallergen, 55% with eczema USA	Severe asthma exacerbations Hospital admissions Pneumonia	Funded by the National Heart Lung and Blood Institute Crossover study design with 16 week treatment periods and no washout between treatments
Szefler 2013 (Szefler et al., 2013)	**Regular ICS** (500 mcg BUD once daily) **Regular montelukast** (4 mg montelukast once daily) 52 weeks	203 infants aged 2-4 years with mild persistent asthma, frequent wheezing episodes, regular symptoms or frequent SABA use (use on ≥3 of 7 days during run-in)	Severe asthma exacerbations Mortality Reliever/rescue medication use Lung function (PEF) Adverse events Pneumonia	Funded by AstraZeneca Secondary analysis of 2007 paper including only those aged 2-4 years

Study	Intervention and comparison	Population	Outcomes	Comments
		Exacerbations: not reported Atopy: not reported USA		

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

First add-on treatment for adults and young people ≥12 years with uncontrolled asthma.

Table 6: Clinical evidence summary: regular low dose ICS/LABA with SABA prn vs regular low dose ICS with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS with SABA prn	Risk difference with Regular ICS/LABA with SABA prn	
Severe asthma exacerbations at 3-5 months (final values, lower is better)	1417 (5 RCTs) Follow-up: 12 weeks	⊕◯◯◯ Very low[a,b,c]	**RR 0.82** (0.46 to 1.45)	45 per 1,000	**8 fewer per 1,000** (24 fewer to 20 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS with SABA prn	Risk difference with Regular ICS/LABA with SABA prn	
Severe asthma exacerbations at ≥6 months (final values, lower is better)	625 (2 RCTs) Follow-up: 24 weeks	⊕◯◯◯ Very low[d,e]	**RD -0.02** (-0.08 to 0.03)	175 per 1,000	**20 fewer per 1,000** (80 fewer to 30 more) No clinical difference	MID clinical importance=30 per 1000, imprecision= OIS; <80% very serious imprecision, 80-90%- serious imprecision, 90% power – no imprecision
Severe exacerbation rate (per patient year, lower is better)	1294 (3 RCTs) Mean follow-up: 29 weeks	⊕◯◯◯ Very low[d,f]	**Rate ratio 0.77** (0.57 to 1.05)	-	-	MID=0.8-1.25
Mortality (final values, lower is better)	1788 (4 RCTs) Mean follow-up: 15 weeks	⊕◯◯◯ Very low[e,g]	**RD 0.00** (-0.01 to 0.00)	1 per 1,000	**1 fewer per 1,000** (1 fewer to 1 fewer) Clinically important benefit of ICS/LABA	MID clinical importance=1 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS with SABA prn	Risk difference with Regular ICS/LABA with SABA prn	
Asthma control (Asthma Control Questionnaire-7, scale range 0-6, change scores, lower is better)	771 (1 RCT) Follow-up: 12 weeks	⨁⨁◯◯ Low[g]	-	The mean change in ACQ was **0.95**	MD **0.22 lower** (0.33 lower to 0.1 lower) No clinical difference	MID=0.5 (established MID)
Hospital admissions at 3-5 months (final values, lower is better)	802 (1 RCT) Follow-up: 12 weeks	⨁◯◯◯ Very low[c,g]	**OR 0.14** (0.00 to 6.92)	2 per 1,000	**2 fewer per 1,000** (2 fewer to 14 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Hospital admissions at ≥6 months (final values, lower is better)	994 (2 RCTs) Mean follow-up: 38 weeks	⨁◯◯◯ Very low[c,d]	**RR 0.85** (0.26 to 2.77)	12 per 1,000	**2 fewer per 1,000** (9 fewer to 21 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS with SABA prn	Risk difference with Regular ICS/LABA with SABA prn	
Reliever/rescue medication use (puffs per day, change scores, lower is better)	1595 (5 RCTs) Mean follow-up: 22 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean change in reliever/rescue medication use was **-1.64**	MD **0.19 lower** (0.28 lower to 0.11 lower) No clinical difference	MID=0.81 (established MID)
Reliever/rescue medication use (SABA-free days, %, mixed values, higher is better)	1937 (6 RCTs) Mean follow-up: 19 weeks	⊕⊕◯◯ Low[h]	-	The mean % of SABA-free days, was **34.9%**	MD **8.73 higher** (5.85 higher to 11.61 higher) No clinical difference	MID=18.5 (calculated as median follow-up SD/2)
Lung function (FEV_1, litres, change scores, higher is better)	2565 (7 RCTs) Mean follow-up: 19 weeks	⊕◯◯◯ Very low[b,h]	-	The mean change in FEV_1 was **0.51 L**	MD **0.13 higher** (0.05 higher to 0.21 higher) No clinical difference	MID=0.23 (established MID)
Lung function (PEF, L/minute, change scores, higher is better)	2231 (5 RCTs) Mean follow-up: 20 weeks	⊕⊕◯◯ Low[h]	-	The mean lung function change in PEF was **16.2 L/minute**	MD **22.5 higher** (18.91 higher to 26.08 higher) Clinically important benefit for ICS/LABA	MID=18.79 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS with SABA prn	Risk difference with Regular ICS/LABA with SABA prn	
Lung function (PEF, % of predicted, change scores, higher is better)	177 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[i,j]	-	The mean change in PEF was **7.6 % of predicted**	MD **6.8 higher** (3.4 higher to 10.2 higher) No clinical difference	MID=5.8 (calculated as mean follow-up SDs/2)
Adverse events (final values, lower is better)	3192 (9 RCTs) Mean follow-up: 18 weeks	⊕⊕◯◯ Low[h]	**RR 0.93** (0.85 to 1.01)	377 per 1,000	**26 fewer per 1,000** (57 fewer to 4 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25
Pneumonia (including respiratory tract infections, final values, lower is better)	2591 (3 RCTs) Mean follow-up: 25 weeks	⊕◯◯◯ Very low[a,c,k]	**OR 0.97** (0.69 to 1.37)	57 per 1,000	**2 fewer per 1,000** (17 fewer to 20 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to concerns arising from the method of randomisation (method not reported) in the majority of the evidence

b. Downgraded by one increment due to heterogeneity that was unexplained by random effects model

c. Downgraded by two increments due to the 95%CI overlapping both the upper and lower MID (0.8-1.25)

d. Downgraded by two increments due to concerns arising from the randomisation process (method not reported) and missing outcome data in the majority of the evidence

e. Downgraded by two increments due to inadequate sample size (power <80%)

f. Downgraded by one increment due to the 95%CI overlapping the lower MID (0.8-1.25)

g. Downgraded by two increments due to concerns arising from the method of randomisation (method not reported) and deviations from the intended interventions (adherence not reported) in the majority of the evidence

h. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended interventions (adherence not reported) and/or missing outcome data in the majority of the evidence

i. Downgraded by one increment due to concerns arising from missing outcome data

j. Downgraded by one increment due to the 95%CI overlapping one MID

k. Downgraded by one increment due to the majority of the evidence being for an outcome that is indirectly relevant to that listed in this review protocol

Table 7: Clinical evidence summary: low dose ICS/formoterol maintenance and reliever therapy (MART) vs regular low dose ICS with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS with SABA prn	Risk difference with ICS/form MART	
Severe asthma exacerbations at ≥6 months (final values, lower is better)	1239 (1 RCT) Follow-up: 6-12 months	⨁⨁◯◯ Low[a,b]	**RR 0.52** (0.35 to 0.75)	117 per 1,000	**56 fewer per 1,000** (76 fewer to 29 fewer) Clinically important benefit for MART	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS with SABA prn	Risk difference with ICS/form MART	
Severe exacerbation rate (final values, lower is better)	697 (1 RCT) Follow-up: 26 weeks	⊕⊕⊕◯ Moderate[a]	**Rate ratio 0.24** (0.20 to 0.27)	-	-	MID=0.8-1.25
Hospital admissions (final values, lower is better)	697 (1 RCT) Follow-up: 26 weeks	⊕⊕⊕◯ Moderate[a]	**RR 0.10** (0.01 to 0.75)	29 per 1,000	**26 fewer per 1,000** (29 fewer to 7 fewer) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Reliever/rescue medication use (puffs per day, final values, lower is better)	697 (1 RCT) Follow-up: 26 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean change in reliever/rescue medication use was **1.48 puffs per day**	MD **0.34 lower** (0.51 lower to 0.17 lower) No clinical difference	MID=0.81 (established MID)
Reliever/rescue medication use (reliever-free days, %, final values, higher is better)	697 (1 RCT) Follow-up: 26 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean change in reliever-free days was **45.4%**	MD **8.1 higher** (2.5 higher to 12.7 higher) No clinical difference	MID=18.9 (calculated as follow-up SD/2)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS with SABA prn	Risk difference with ICS/form MART	
Lung function (FEV_1, litres, change scores, higher is better)	1239 (1 RCT) Follow-up: 6-12 months	⊕⊕◯◯ Low[a,b]	-	The mean change in FEV_1 was **0.11 L**	MD **0.1 higher** (0.07 higher to 0.13 higher) No clinical difference	MID=0.23 (established MID)
Lung function (PEF, L/minute, final values, higher is better)	697 (1 RCT) Follow-up: 26 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean change in PEF was **345 L/minute**	MD **25 higher** (19.4 higher to 30.6 higher) Clinically important benefit for MART	MID=18.79 (established MID)
Adverse events (final values, lower is better)	697 (1 RCT) Follow-up: 26 weeks	⊕⊕◯◯ Low[a,c]	**RR 0.93** (0.71 to 1.21)	249 per 1,000	**17 fewer per 1,000** (72 fewer to 52 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS with SABA prn	Risk difference with ICS/form MART	
Pneumonia (respiratory tract infections, final values, lower is better)	697 (1 RCT) Follow-up: 26 weeks	⨁◯◯◯ Very low[a,d,e]	**RR 0.95** (0.67 to 1.34)	158 per 1,000	**8 fewer per 1,000** (52 fewer to 54 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)

b. Downgraded by one increment due to intervention indirectness - evidence from a post-hoc analysis that included studies that treated participants with moderate-dose ICS

c. Downgraded by one increment due to the 95%CI overlapping the lower MID (0.8-1.25)

d. Downgraded by one increment due to the outcome reported in the paper not being directly relevant to the outcome listed in this review protocol (respiratory tract infections reported, not pneumonia events)

e. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

Table 8: Clinical evidence summary: low dose ICS/Formoterol maintenance and reliever therapy (MART) vs regular low dose ICS/LABA with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS/LABA with SABA prn	Risk difference with ICS/form MART	
Severe asthma exacerbations at ≥6 months (final values, lower is better)	4336 (2 RCTs) Follow-up: 12 months	⊕⊕⊕◯ Moderate[a]	**RR 0.67** (0.59 to 0.76)	217 per 1,000	**72 fewer per 1,000** (89 fewer to 52 fewer) Clinically important benefit for MART	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Severe exacerbation rate (per patient year, lower is better)	4336 (2 RCTs) Follow-up: 12 months	⊕⊕⊕◯ Moderate[a]	**Rate ratio 0.62** (0.55 to 0.70)	-	**-**	MID=0.8-1.25
Mortality (final values, lower is better)	2091 (1 RCT) Follow-up: 12 months	⊕◯◯◯ Very low[b,c]	**RR 0.99** (0.06 to 15.86)	1 per 1,000	**0 fewer per 1,000** (1 fewer to 14 more) No clinical difference	MID clinical importance=1 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS/LABA with SABA prn	Risk difference with ICS/form MART	
Asthma control (Asthma Control Questionnaire, scale range: 0-6, final values, lower is better)	1888 (2 RCTs) Follow-up: 12 months	⊕⊕⊕◯ Moderate[a]	-	The mean ACQ score was **1.29**	MD **0.14 lower** (0.19 lower to 0.1 lower) No clinical difference	MID=0.5 (established MID)
Hospital admissions at ≥6 months (final values, lower is better)	2091 (1 RCT) Follow-up: 12 months	⊕⊕⊕◯ Moderate[b]	**RR 0.33** (0.17 to 0.65)	32 per 1,000	**21 fewer per 1,000** (26 fewer to 11 fewer) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Reliever/rescue medication use (puffs per day, change scores, lower is better)	4336 (2 RCTs) Follow-up: 12 months	⊕⊕⊕◯ Moderate[a]	-	The mean change in reliever/rescue use was **-0.90 puffs per day**	MD **0.22 lower** (0.28 lower to 0.15 lower) No clinical difference	MID=0.81 (established MID)
Reliever/rescue medication use (reliever-free days, %, change scores, higher is better)	2060 (1 RCT) Follow-up: 12 months	⊕⊕⊕◯ Moderate[b]	-	The mean change in reliever-free days was **37.2%**	MD **4.4 higher** (1.6 higher to 7.2 higher) No clinical difference	MID=16.2 (calculated as follow-up SD/2)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with Regular ICS/LABA with SABA prn	Risk difference with ICS/form MART	
Lung function (FEV_1, litres, change scores, higher is better)	4336 (2 RCTs) Follow-up: 12 months	⊕⊕⊕◯ Moderate[b]	-	The mean change in FEV_1 was **0.08 L**	MD **0.06 higher** (0.04 higher to 0.08 higher) No clinical difference	MID=0.23 (established MID)
Lung function (PEF, litres per minute, change scores, higher is better)	4336 (2 RCTs) Follow-up: 12 months	⊕⊕⊕◯ Moderate[a]	-	The mean change in PEF was **14.7 L/minute**	MD **6.75 higher** (4.28 higher to 9.21 higher) No clinical difference	MID=18.79 (established MID)
Adverse events (final values, lower is better)	2091 (1 RCT) Follow-up: 12 months	⊕⊕⊕◯ Moderate[b]	**RR 1.00** (0.93 to 1.07)	575 per 1,000	**0 fewer per 1,000** (40 fewer to 40 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to concerns arising from the randomisation process (method not reported) in the majority of the evidence

b. Downgraded by one increment due to concerns arising from deviations from the intended interventions (adherence to study treatments not reported) in the majority of the evidence

c. Downgraded by two increments due to the 95%CI overlapping both the upper and lower MID (0.8-1.25)

Further step-up treatment for adults and young people ≥12 years with uncontrolled asthma.

Table 8 Clinical evidence summary: ICS/formoterol maintenance and reliever therapy (MART) vs regular moderate/high dose ICS/LABA with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS/LABA with SABA prn	Risk difference with ICS/form MART	
Severe asthma exacerbations at ≥6 months (final values, lower is better)	8148 (5 RCTs) Mean follow-up: 35 weeks	⊕⊕⊕◯ Moderate[a]	**Peto OR 0.72** (0.63 to 0.83)	140 per 1,000	**35 fewer per 1,000** (47 fewer to 21 fewer) Clinically important benefit for MART	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Severe exacerbation rate (final values, lower is better)	6069 (4 RCTs) Mean follow-up: 7.5 months	⊕⊕⊕◯ Moderate[a]	**Rate ratio 0.70** (0.61 to 0.81)	-	**-**	MID=0.8-1.25
Mortality (final values, lower is better)	8212 (5 RCTs) Mean follow-up: 36 weeks	⊕⊕◯◯ Low[b]	RD 0.00 (0.00-0.00	1 per 1,000	**1 fewer per 1,000** (1 fewer to 1 fewer) Clinically important benefit for MART?	MID clinical importance=1 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS/LABA with SABA prn	Risk difference with ICS/form MART	
Quality of life (Asthma Quality of Life Questionnaire with standard activities, scale range: 1-7, change scores, higher is better)	2143 (1 RCT) Follow-up: 24 weeks	⊕◯◯◯ Very low[c,d]	-	The mean change in AQLQ was **0.57**	MD **0.03 higher** (0.06 lower to 0.12 higher) No clinical difference	MID= 0.5 (established MID)
Asthma control (Asthma Control Questionnaire, scale range: 1-6, final values, lower is better)	4750 (3 RCTs) Mean follow-up: 34 weeks	⊕⊕⊕⊕ High	-	The mean ACQ score was **1.30**	MD **0.05 lower** (0.09 lower to 0) No clinical difference	MID= 0.5 (established MID)
Hospital admissions at ≥6 months (final values, lower is better)	2579 (2 RCTs) Mean follow-up: 25 weeks	⊕⊕⊕◯ Moderate[a]	**RR 0.67** (0.46 to 0.99)	54 per 1,000	**16 fewer per 1,000** (25 fewer to 0 fewer) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Reliever/rescue medication use (puffs per day, final values, lower is better)	4642 (4 RCTs) Mean follow-up: 45 weeks	⊕◯◯◯ Very low[e,f]	-	The mean number of puffs per day was **5.6**	MD **0.51 lower** (1.14 lower to 0.11 higher) No clinical difference	MID= 0.81 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS/LABA with SABA prn	Risk difference with ICS/form MART	
Lung function (FEV_1, litres, change scores, higher is better)	2143 (1 RCT) Follow-up: 52 weeks	⊕◯◯◯ Very low[c,d]	-	The mean change in FEV_1 was **0.14 L**	MD **0.03 higher** (0 to 0.06 higher) No clinical difference	MID= 0.23 (established MID)
Lung function (FEV_1, % of predicted, final values, higher is better)	303 (1 RCT) Follow-up: 24 weeks	⊕◯◯◯ Very low[g,h]	-	The mean FEV_1 was **84.1% of predicted**	MD **3 higher** (1.43 lower to 7.43 higher) No clinical difference	MID=9.85 (calculated as baseline SD/2)
Lung function (PEF, litres per minute, final values, higher is better)	2304 (1 RCT) Follow-up: 26 weeks	⊕⊕⊕⊕ High	-	The mean PEF was **359.4 L/min**	MD **0.8 lower** (4.4 lower to 2.8 higher) No clinical difference	MID= 18.79 (established MID)
Adverse events (final values, lower is better)	4447 (2 RCTs) Mean follow-up: 39 weeks	⊕⊕⊕⊕ High	**RR 0.97** (0.88 to 1.06)	247 per 1,000	**7 fewer per 1,000** (30 fewer to 15 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to the 95%CI overlapping one MID (0.8-1.25)

b. Downgraded by two increments: optimal information size<80% using https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html

c. Downgraded by two increments due to high risk of bias (up/down titration allowed at week 4 onwards plus addition of other asthma controller medication was allowed and study was open-label; deviation from inclusion criteria (inclusion of people with higher and lower FEV1 than pre-scpecified))

d. Downgraded by one increment due to intervention indirectness - ICS dose could be down-titrated to low-dose rather than moderate-dose at investigators discretion

e. Downgraded by two increments due to substantial heterogeneity not explained by subgroup analysis or random effects model (I sq.=97%)

f. Downgraded by one increment due to the 95%CI overlapping one MID

g. Downgraded by two increments due to concerns arising from deviations from the intended interventions (unbalanced use of oral prednisolone between study arms and no adherence monitoring for maintenance therapy included)

h. Downgraded by one increment due to population indirectness (15% of participants did not have asthma that was uncontrolled at screening)

Table 9 Clinical evidence summary: ICS/formoterol maintenance and reliever therapy (MART) vs regular moderate/high dose ICS with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS with SABA with SABA prn	Risk difference with ICS/form MART	
Severe asthma exacerbations at ≥6 months (final values, lower is better)	3737 (2 RCTs) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	RR 0.61 (0.53 to 0.71)	233 per 1,000	**81 fewer per 1,000** (96 fewer to 60 fewer) Clinically important benefit for MART	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS with SABA with SABA prn	Risk difference with ICS/form MART	
Severe exacerbation rate (final values, lower is better)	1890 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	**Rate ratio 0.57** (0.48 to 0.68)	-	**-**	MID=0.8-1.25
Mortality (final values, lower is better)	1890 (1 RCT) Follow-up: 52 weeks	⊕◯◯◯ Very low[a,b]	**RR 0.50** (0.05 to 5.48)	2 per 1,000	**1 fewer per 1,000** (2 fewer to 10 more) Clinically important benefit for MART?	MID clinical importance=1 per 1000, imprecision=0.8-1.25
Reliever/rescue medication use (daytime SABA use, puffs per day, final values, lower is better)	1847 (1 RCT) Follow-up: 24 weeks	⊕◯◯◯ Very low[c,d]	-	The mean number of puffs per day was **0.84**	MD **0.3 lower** (0.37 lower to 0.23 lower) No clinical difference	MID= 0.81 (established MID)
Reliever/rescue medication use (nighttime SABA use, puffs per night, final values, lower is better)	1847 (1 RCT) Follow-up: 24 weeks	⊕◯◯◯ Very low[c,d]	-	The mean number of puffs per night was **0.37**	MD **0.15 lower** (0.2 lower to 0.1 lower) No clinical difference	MID= 0.81 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS with SABA with SABA prn	Risk difference with ICS/form MART	
Reliever/rescue medication use (% SABA-free days, change scores, higher is better)	1890 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean percentage of SABA-free days was **34.0**	MD **11 higher** (8.2 higher to 13.8 higher) No clinical difference	MID=15.52 (calculated as final SD/2)
Lung function (FEV_1, litres, change scores, higher is better)	1847 (1 RCT) Follow-up: 24 weeks	⊕◯◯◯ Very low[c,d]	-	The mean change in FEV_1 was **2.43 L**	MD **0.1 higher** (0.05 higher to 0.15 higher) No clinical difference	MID= 0.23 (established MID)
Lung function (PEF L/min, change scores, higher is better)	3741 (2 RCTs) Mean follow-up: 38 weeks	⊕⊕◯◯ Low[a,e]	-	The mean PEF was **343.75 L/min**	MD **18.86 higher** (15.76 higher to 21.96 higher) Clinically important benefit for MART	MID=18.79 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS with SABA with SABA prn	Risk difference with ICS/form MART	
Adverse events (final values, lower is better)	3737 (2 RCTs) Mean follow-up: 38 weeks	⊕⊕⊕◯ Moderate[a]	**RR 0.96** (0.91 to 1.02)	568 per 1,000	**23 fewer per 1,000** (51 fewer to 11 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25
Pneumonia (final values, lower is better)	1847 (1 RCT) Follow-up: 24 weeks	⊕◯◯◯ Very low[d,f,g]	**RR 0.87** (0.72 to 1.06)	197 per 1,000	**26 fewer per 1,000** (55 fewer to 12 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to concerns arising from deviations from the intended intervention (397 protocol deviations in 309 participants)

b. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

c. Downgraded by two increments due to concerns arising from the randomisation method (not reported), deviations from the intended interventions (85% adherence to maintenance medication) and missing outcome data (attrition rates not reported)

d. Downgraded by one increment due to population indirectness (12% of participants were aged 4-11 years)

e. Downgraded by one increment due to the 95%CI overlapping one MID (published MID=18.79 L/min)

f. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended intervention (85% adherence to maintenance medication) and missing outcome data (dropout rate not reported)

g. Downgraded by one increment due to the 95%CI overlapping one MID (0.8-1.25)

Table 10 Clinical evidence summary: Regular moderate/high dose ICS/LABA with SABA prn vs regular low/moderate dose ICS/LABA plus montelukast with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS/LABA plus montelukast	Risk difference with ICS/LABA	Comments
Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)	61 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[a]	-	The mean ACT score was **23.5**	MD **1.38 higher** (1.16 higher to 1.6 higher) No clinical difference	MID=3 (established MID)
Inflammatory markers (FeNO, ppb, final values, lower is better)	61 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[b]	-	The mean FeNO was **21.13 ppb**	MD **6.75 lower** (10.25 lower to 3.25 lower) No clinical difference	MID=11.35 (calculated as baseline SD/2)

a. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended intervention (open label study with no information on switching between study arms, adherence to maintenance therapy or co-interventions), measurement of the outcome (subjective outcome measure with knowledge of the intervention received) and selection of the reported result (inadequate information on analysis method used)

b. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended intervention (open label study with no information on switching between study arms, adherence to maintenance therapy or co-interventions) and selection of the reported result (inadequate information on analysis method used)

Table 11 Clinical evidence summary: Regular low/moderate dose ICS/LABA plus LAMA with SABA prn vs regular moderate/high dose ICS/LABA with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS/LABA plus LAMA	Risk difference with ICS/LABA with SABA	
Severe asthma exacerbations at ≥6 months (final values, lower is better)	3625 (2 RCTs) Follow-up: 52 weeks	⊕◯◯◯ Very low[a,b]	**RR 0.89** (0.77 to 1.02)	181 per 1,000	**20 fewer per 1,000** (42 fewer to 4 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Mortality (final values, lower is better)	5249 (3 RCTs) Mean follow-up: 43 weeks	⊕◯◯◯ Very low[a,c,d]	**OR 0.63** (0.21 to 1.87)	3 per 1,000	**1 fewer per 1,000** (2 fewer to 3 more) Clinically important benefit of ICS/LABA	MID clinical importance=1 per 1000, imprecision=0.8-1.25
Quality of life (Asthma Quality of Life Questionnaire, scale range 1-7, change scores, higher is better)	2475 (1 RCT) Follow-up: 52 weeks	⊕⊕◯◯ Low[a]	-	The mean change in Asthma Quality of Life Questionnaire score was **0.83**	MD **0.01 lower** (0.08 lower to 0.06 higher) No clinical difference	MID=0.5 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS/LABA plus LAMA	Risk difference with ICS/LABA with SABA	
Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)	63 (1 RCT) Follow-up: 24 weeks	⊕⊕◯◯ Low[a]	-	The mean Asthma Control Test score was **24.0**	MD **0.44 lower** (0.81 lower to 0.07 lower) No clinical difference	MID=3 (established MID)
Reliever/rescue medication use (puffs per day, change scores, lower is better)	2475 (1 RCT) Follow-up: 52 weeks	⊕⊕◯◯ Low[a]	-	The mean change in daily reliever use was **0.90 puffs per day**	MD **0.05 lower** (0.16 lower to 0.06 higher) No clinical difference	MID=0.81 puffs/day (established MID)
Reliever/rescue medication use (SABA-free days, %, change scores, higher is better)	2475 (1 RCT) Follow-up: 52 weeks	⊕⊕◯◯ Low[a]	-	The mean % of SABA-free days was **23.35%**	MD **0.11 higher** (2.47 lower to 2.69 higher) No clinical difference	MID=16.36 (calculated as final SD/2)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS/LABA plus LAMA	Risk difference with ICS/LABA with SABA	
Lung function (FEV_1, mL, change scores, higher is better)	1149 (1 RCT) Follow-up: 26 weeks	⊕⊕⊕◯ Moderate[e]	-	The mean change in FEV_1 was **127 mL**	MD **58 higher** (99.75 higher to 16.25 higher) Clinically important benefit of ICS/LABA	MID=0.23 L (23 mL) (established MID)
Lung function (PEF, L/min, change scores, higher is better)	1149 (1 RCT) Follow-up: 26 weeks	⊕⊕⊕◯ Moderate[e]	-	The mean change in PEF was **-3.1 L/min**	MD **8.4 higher** (13.21 higher to 3.59 higher) No clinical difference	MID=18.79 L/min (established MID)
Adverse events (final values, lower is better)	5249 (3 RCTs) Mean follow-up: 43 weeks	⊕⊕◯◯ Low[e,f]	**RR 1.00** (0.97 to 1.04)	701 per 1,000	**0 fewer per 1,000** (21 fewer to 28 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with ICS/LABA plus LAMA	Risk difference with ICS/LABA with SABA	
Pneumonia (final values, lower is better)	5249 (3 RCTs) Mean follow-up: 43 weeks	⊕◯◯◯ Very low[a,g]	not estimable	9 per 1,000	**9 fewer per 1,000** (9 fewer to 9 fewer) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25
Inflammatory markers (FeNO, ppb, final values, lower is better)	63 (1 RCT) Follow-up: 24 weeks	⊕◯◯◯ Very low[a,h]	-	The mean FeNO was **14.37 ppb**	MD **15.63 higher** (10.89 higher to 20.37 higher) Clinically important benefit of ICS/LABA plus LAMA	MID=13.34 (calculated as baseline SD/2)

a. Downgraded by two increments due to concerns arising from deviations from the intended intervention (no adherence monitoring included) and missing outcome data (12% missing data with reasons for discontinuation related to participant's health status)

b. Downgraded by one increment due to the 95%CI overlapping one MID (0.8-1.25)

c. Downgraded by one increment due to visual assessment of heterogeneity

d. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

e. Downgraded by one increment due to concerns arising from deviations from the intended intervention (no adherence monitoring included)

f. Downgraded by one increment due to moderate heterogeneity (I.sq=49%)

g. Downgraded by two increments due to inadequate power (6%)

h. Downgraded by one increment due to the 95%CI overlapping one MID

Table 12 Clinical evidence summary: Regular moderate/high dose ICS/LABA with SABA prn vs regular moderate/high dose ICS with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Severe asthma exacerbations at 3-5 months (final values, lower is better)	3728 (10 RCTs) Follow-up: 12 weeks	⊕◯◯◯ Very low[a,b,c]	**RR 0.73** (0.51 to 1.04)	35 per 1,000	**10 fewer per 1,000** (17 fewer to 1 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Severe asthma exacerbations at ≥6 months (final values, lower is better)	8067 (10 RCTs) Mean follow-up: 45 weeks	⊕⊕◯◯ Low[a]	**Peto OR 0.70** (0.61 to 0.80)	179 per 1,000	**47 fewer per 1,000** (62 fewer to 30 fewer) Clinically important benefit for ICS/LABA	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Severe exacerbation rate (final values, lower is better)	4514 (5 RCTs) Mean follow-up: 52 weeks	⊕⊕◯◯ Low[b,d]	**Rate ratio 0.74** (0.65 to 0.84)	-	-	MID=0.8-1.25
Mortality (final values, lower is better)	9508 (14 RCTs) Mean follow-up: 33 weeks	⊕◯◯◯ Very low[e,f]	not estimable	1 per 1,000	**1 fewer per 1,000** (1 fewer to 1 fewer) Clinically important benefit for ICS/LABA	MID clinical importance=1 per 1000, imprecision=0.8-1.25
Quality of life (Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)	4521 (7 RCTs) Mean follow-up: 19 weeks	⊕⊕◯◯ Low[g]	-	The mean AQLQ score was **0.77**	MD **0.14 higher** (0.08 higher to 0.21 higher) No clinical difference	MID= 0.5 (established MID)
Asthma control (Asthma Control Test, scale range: 5-25, mixed values, higher is better)	2892 (6 RCTs) Mean follow-up: 21 weeks	⊕⊕◯◯ Low[h]	-	The mean ACT score was **18.59**	MD **0.88 higher** (0.6 higher to 1.16 higher) No clinical difference	MID=3 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Asthma control (Asthma control questionnaire-7, scale range: 0-6, change scores, lower is better)	1373 (1 RCT) Follow-up: 21 months	⊕⊕⊕⊕ High	-	The mean change in ACQ score was **-0.32**	MD **0.23 lower** (0.3 lower to 0.16 lower) No clinical difference	MID=0.5 (established MID)
Hospital admissions at ≥6 months (final values, lower is better)	2522 (2 RCTs) Follow-up: 52 weeks	⊕◯◯◯ Very low[d,i,j]	**RR 0.46** (0.07 to 2.84)	10 per 1,000	**5 fewer per 1,000** (9 fewer to 18 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Reliever/rescue medication use (puffs per day, change scores, lower is better)	2402 (8 RCTs) Mean follow-up: 17 weeks	⊕⊕◯◯ Low[h]	-	The mean change in reliever use was **-0.77 puffs per day**	MD **0.49 lower** (0.62 lower to 0.36 lower) No clinical difference	MID= 0.81 (established MID)
Reliever/rescue medication use (reliever free days or % of days, change scores, higher is better)	3556 (9 RCTs) Mean follow-up: 22 weeks	⊕◯◯◯ Very low[a,i]	-	-	SMD **0.28 SD higher** (0.17 higher to 0.38 higher) No clinical difference	MID= 0.5 (standard MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Lung function (FEV_1, litres, mixed values, higher is better)	7791 (12 RCTs) Mean follow-up: 28 weeks	⊕◯◯◯ Very low[a,i]	-	The mean FEV_1 was **2.35 L**	MD **0.11 higher** (0.09 higher to 0.12 higher) No clinical difference	MID= 0.23 (established MID)
Lung function (FEV_1, % of predicted, mixed values, higher is better)	1752 (6 RCTs) Mean follow-up: 28 weeks	⊕◯◯◯ Very low[k,l]	-	The mean FEV_1 was **68.66% of predicted**	MD **0.38 higher** (0 to 0.76 higher) No clinical difference	MID=3.33 (calculated as baseline SDs/2)
Lung function (PEF, L/min, mixed values, higher is better)	5941 (16 RCTs) Mean follow-up: 24 weeks	⊕◯◯◯ Very low[a,i]	-	The mean PEF was **370.35 L/min**	MD **24.31 higher** (19.83 higher to 28.78 higher) Clinically important benefit for ICS/LABA	MID= 18.79 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Adverse events (final values, lower is better)	10713 (16 RCTs) Mean follow-up: 30 weeks	⊕⊕⊕◯ Moderate[m]	**RR 0.97** (0.94 to 1.00)	572 per 1,000	**17 fewer per 1,000** (34 fewer to 0 fewer) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25
Pneumonia (including respiratory tract infections, final values, lower is better)	7399 (11 RCTs) Mean follow-up: 32 weeks	⊕◯◯◯ Very low[e,f]	**RD -0.01** (-0.02 to 0.00)	26 per 1,000	**10 more per 1,000** (0 fewer to 20 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25
Adrenal insufficiency (cortisol/creatinine ratio, change scores, lower is better)	201 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[l,n]	-	The mean change in cortisol/creatinine ratio **-13.38**	MD **16.86 higher** (7.37 higher to 26.35 higher) No clinical difference	MID=17.03 (calculated as final SD/2)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Adrenal insufficiency (serum cortisol, 0-24h AUC, change scores, higher is better)	57 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[l,o]	-	The mean change in serum cortisol was **0.8**	MD **0.2 higher** (0.02 higher to 0.38 higher) Clinically important benefit for ICS/LABA	MID=0.175 (calculated as final SD/2)
Adrenal insufficiency (morning cortisol <5 mcg/dL, final values, lower is better)	162 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[j,p]	**RR 0.50** (0.05 to 5.41)	25 per 1,000	**12 fewer per 1,000** (23 fewer to 109 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by two increments because the majority of evidence is at high risk of bias (no adherence monitoring reported or low; randomisation method not reported; high dropout rate with no information on rates per group or reasons for discontinuation or reasons for discontinuation related to participant's health status).

b. Downgraded by one increment because 95% CI crosses one MID (0.8-1.25)

c. Asymmetry detected in funnel plot suggests publication bias.

d. Downgraded by one increment due concerns about risk of bias in the majority of studies due to deviations from the intended interventions (no information on adherence to interventions)

e. Downgraded by one increment due to some concerns about risk of bias in the majority of studies (due to no adherence monitoring; unclear information about randomisation and high dropout rate with reasons for discontinuation related to participant's health status)

f. Downgraded by two increments: optimal information size<80% using https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html

g. Downgraded by two increments because the majority of evidence is at high risk of bias (Adherence not reported or low; high dropout rate and reasons for discontinuation related to participant's health status

h. Downgraded by two increments because the majority of evidence is at high risk of bias (Adherence not reported or low; high dropout rate and reasons for discontinuation related to participant's health status; randomisation method not reported)

i. Downgraded by one increment due to unexplained heterogeneity

j. Downgraded by two increments because 95% CI crosses both MIDs (0.8-1.25)

k. Downgrade by two increments because the majority of evidence is at high risk of bias (randomisation method not reported; includes an unblinded trial with no information on switching between groups or co-interventions; adherence not reported or 86.7%; high dropout rate with reasons related to participant's health status or no information of rates per study arm.

l. Downgraded by one increment because 95%cI crosses one MID (calculated as baseline SD (of intervention + control groups/2)/2=0.5)

m. Downgraded by one increment due to some concerns about risk of bias in the majority of studies (due to no adherence monitoring; lack of information about randomisation and high dropout rate with reasons for discontinuation related to participant's health status)

n. Downgraded by two increments because the study is at high risk of bias (randomisation method not reported and no adherence monitoring)

o. Downgraded by two increments because the study was at high risk of bias (randomisation method not reported and no information on dropout rate from 15% subset of participants who had cortisol measured)

p. Downgraded by two increments because the study was at high risk of bias (randomisation method not reported, 22% missing data, 11% difference in missing data rates between study arms and reasons for discontinuation related to participant's health status)

Table 13 Clinical evidence summary: Regular moderate/high dose ICS/LABA with SABA prn vs regular low/moderate dose ICS plus montelukast with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with regular ICS plus montelukast	Risk difference with regular ICS/LABA	Comments
Severe asthma exacerbations at 3-5 months (final values, lower is better)	948 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[a,b,c]	**RR 1.12** (0.65 to 1.94)	49 per 1,000	**6 more per 1,000** (17 fewer to 46 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with regular ICS plus montelukast	Risk difference with regular ICS/LABA	Comments
Severe exacerbation rate (final values, lower is better)	948 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[a,b,c]	**Rate ratio 1.12** (0.64 to 1.93)	-	-	MID=0.8-1.25
Mortality (final values, lower is better)	361 (1 RCT) Follow-up: 104 weeks	⊕◯◯◯ Very low[d,e,f]	**RD 0.00** (-0.01 to 0.01)	0 per 1,000	**0 fewer per 1,000** (10 fewer to 10 more) No clinical difference	MID clinical importance=1 per 1000, imprecision=0.8-1.25
Quality of life (Asthma Quality of Life Questionnaire, scale range 1-7, mixed values, higher is better)	350 (1 RCT) Follow-up: 104 weeks	⊕◯◯◯ Very low[e,g]	-	The mean AQLQ score was **5.43**	MD **0.01 lower** (0.24 lower to 0.22 higher) No clinical difference	MID=0.5 (established MID)
Quality of life (EQ-5D, scale range: 0-1, final values, higher is better)	330 (1 RCT) Follow-up: 104 weeks	⊕◯◯◯ Very low[e,g,h]	-	The mean EQ-5D score was **0.807**	MD **0.01 lower** (0.07 lower to 0.05 higher) No clinical difference	MID=0.03 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with regular ICS plus montelukast	Risk difference with regular ICS/LABA	Comments
Asthma control (Asthma Control Questionnaire, scale range: 0-6, final values, lower is better)	350 (1 RCT) Follow-up: 104 weeks	⊕◯◯◯ Very low[e,g]	-	The mean ACQ score was **1.31**	MD **0.03 higher** (0.17 lower to 0.23 higher) No clinical difference	MID=0.5 (established MID)
Hospital admissions at ≥6 months (final values, lower is better)	361 (1 RCT) Follow-up: 104 weeks	⊕◯◯◯ Very low[c,d,e]	**RR 1.59** (0.38 to 6.54)	17 per 1,000	**10 more per 1,000** (11 fewer to 94 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Reliever/rescue medication use (puffs per day, change scores, lower is better)	900 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[a,b]	-	The mean change in puffs per day was **-1.66**	MD **0.24 lower** (0.53 lower to 0.05 higher) No clinical difference	MID=0.81 puffs/day (established MID)
Reliever/rescue medication use (nighttime reliever use, final values, lower is better)	162 (1 RCT) Follow-up: 104 weeks	⊕◯◯◯ Very low[e,i]	-	The mean nighttime reliever use was **0.69 puffs per night**	MD **0.06 lower** (0.36 lower to 0.24 higher) No clinical difference	MID=0.61 (calculated as baseline SD/2)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with regular ICS plus montelukast	Risk difference with regular ICS/LABA	Comments
Reliever/rescue medication use (daytime reliever use, final values, lower is better)	179 (1 RCT) Follow-up: 104 weeks	⊕◯◯◯ Very low[e,i]	-	The mean daytime reliever use was **1.89 puffs per day**	MD **0.4 lower** (1 lower to 0.2 higher) No clinical difference	MID=1.15 (calculated as baseline SD/2)
Lung function (PEF, L/min, mixed values, higher is better)	181 (1 RCT) Follow-up: 104 weeks	⊕◯◯◯ Very low[d,e,j]	-	The mean PEF was **395.6 L/min**	MD **24.2 higher** (5.6 lower to 54 higher) Clinically important benefit for ICS/LABA	MID=18.79 L/min (established MID)
Pneumonia (final values, lower is better)	948 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[a,b,c]	**Peto OR 0.13** (0.00 to 6.76)	2 per 1,000	**0 fewer per 1,000** (10 fewer to 0 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended intervention (switching rates between study groups not reported and adherence not monitored) and selection of the reported result (inadequate information on statistical methods used)

b. Downgraded by one increment due to intervention indirectness - participants had interventions added on to their current ICS therapy which could have been low, moderate or high dose

c. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

d. Downgraded by two increments due to concerns arising from deviations from the intended intervention (adherence monitoring not included), and missing outcome data (>10% missing with reasons for discontinuation related to participant's health status)

e. Downgraded by two increments due to intervention indirectness - participants could have been treated with montelukast or zafirlukast with no information on number given each, and flexible ICS dosing with the possibility of removal of regular ICS

f. Downgraded due to inadequate power

g. Downgraded by two increments due to concerns arising from deviations from the intended intervention (86% adherence to maintenance therapy and use of additional therapies in 31% of participants) and measurement of the outcome (subjective outcome measure assessed in an open label study)

h. Downgraded by two increments due to the 95%CI overlapping both MIDs

i. Downgraded by two increments due to concerns arising from deviations from the intended intervention (86% adherence to maintenance therapy and use of additional therapies in 31% of participants)

j. Downgraded by one increment due to the 95%CI overlapping one MID

Table 14 Clinical evidence summary: Regular low/moderate dose ICS/LABA plus montelukast with SABA prn vs regular low/moderate dose ICS/LABA plus LAMA with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS/LABA plus LAMA	Risk difference with ICS/LABA plus montelukast	Comments
Severe asthma exacerbations at ≥6 months (final values, lower is better)	57 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[a,b]	**RR 1.24** (0.43 to 3.61)	172 per 1,000	**41 more per 1,000** (98 fewer to 450 more) Clinically important benefit for ICS/LABA + LAMA	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Quality of life (Asthma Quality of Life Questionnaire, symptom domain, scale range: 0-7, change scores, higher is better)	57 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[a,b]	-	The mean change in AQLQ (symptom domain) was **0.5**	MD **0** (0.52 lower to 0.52 higher) No clinical difference	MID=0.5 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS/LABA plus LAMA	Risk difference with ICS/LABA plus montelukast	Comments
Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)	64 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[c]	-	The mean ACT score was **24.44**	MD **0.94 lower** (1.33 lower to 0.55 lower) No clinical difference	MID=3 (established MID)
Lung function (FEV_1, % of predicted, change scores, higher is better)	57 (1 RCT) Follow-up: 48 weeks	⊕⊕◯◯ Low[a]	-	The mean change in FEV_1 was **8.4% of predicted**	MD **3 lower** (4.85 lower to 1.15 lower) Clinically important benefit for ICS/LABA + LAMA	MID=1.78 (calculated as final SD/2)
Inflammatory markers (FeNO, ppb, mixed values, lower is better)	121 (2 RCTs) Mean follow-up: 30 weeks	⊕◯◯◯ Very low[a,d,e]	-	The mean FeNO was **30.01 ppb**	MD **5.4 lower** (11.29 lower to 0.50 higher) No clinical difference	MID=6.67 (calculated as final SD/2)

a. Downgraded by two increments due to concerns arising from selection of the reported result (inadequate information on statistical methods used), deviations from the intended intervention (adherence not monitored), missing outcome data (15% missing with no information on dropout rates per arm or reasons for discontinuation)

b. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

c. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended intervention (open label study with no information on switching between study arms, adherence to maintenance therapy or co-interventions), measurement of the outcome (subjective outcome measure with knowledge of the intervention received) and selection of the reported result (inadequate information on analysis method used)

d. MID calculated as baseline SD (of intervention + control groups in both studies/4)/2 = 6.67

e. Downgraded by one increment due to unexplained heterogeneity

Table 15 Clinical evidence summary: Regular moderate/high dose ICS/LABA with SABA prn vs regular low/moderate dose ICS plus LAMA with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS plus LAMA	Risk difference with ICS/LABA with SABA	Comments
Severe asthma exacerbations at 3-5 months (final values, lower is better)	262 (1 RCT) Follow-up: 16 weeks	⊕◯◯◯ Very low[a,b]	**RR 1.01** (0.54 to 1.92)	125 per 1,000	**1 more per 1,000** (57 fewer to 115 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Severe asthma exacerbations at ≥6 months (final values, lower is better)	1577 (1 RCT) Follow-up: 24 weeks	⊕◯◯◯ Very low[c,d,e]	**RR 1.23** (0.81 to 1.87)	51 per 1,000	**12 more per 1,000** (10 fewer to 45 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Mortality (final values, lower is better)	325 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[c,f,g]	**RD 0.00** (-0.01 to 0.01)	0 per 1,000	**0 fewer per 1,000** (10 fewer to 10 more) No clinical difference	MID clinical importance=1 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS plus LAMA	Risk difference with ICS/LABA with SABA	Comments
Quality of life (Mini Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)	262 (1 RCT) Follow-up: 16 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean change in mini AQLQ score was **0.13**	MD **0.15 higher** (0.03 lower to 0.33 higher) No clinical difference	MID=0.5 (established MID)
Hospital admissions at 3-5 months (final values, lower is better)	262 (1 RCT) Follow-up: 16 weeks	⊕⊕◯◯ Low[a,e]	**OR 7.23** (1.01 to 51.93)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Hospital admissions at ≥6 months (final values, lower is better)	325 (1 RCT) Follow-up: 24 weeks	⊕◯◯◯ Very low[b,c,f]	**RR 0.39** (0.05 to 3.30)	23 per 1,000	**14 fewer per 1,000** (22 fewer to 53 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Reliever/rescue medication use (puffs per day, change scores, lower is better)	262 (1 RCT) Follow-up: 16 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean change in reliever use was **-0.07 puffs per day**	MD **0.2 lower** (0.72 lower to 0.32 higher) No clinical difference	MID=0.81 puffs/day (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with ICS plus LAMA	Risk difference with ICS/LABA with SABA	Comments
Lung function (FEV_1, litres, change scores, higher is better)	262 (1 RCT) Follow-up: 16 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean change in FEV_1 was **0.04 L**	MD **0.02 higher** (0.06 lower to 0.1 higher) No clinical difference	MID=0.23 L (established MID)
Lung function (PEF, L/min, change scores, higher is better)	262 (1 RCT) Follow-up: 16 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean change in PEF was **0.01 L/min**	MD **0.02 lower** (0.1 lower to 0.06 higher) No clinical difference	MID=18.79 L/min (established MID)
Adverse events (final values, lower is better)	1839 (2 RCTs) Mean follow-up: 20 weeks	⊕⊕◯◯ Low[c,d]	**RR 0.96** (0.87 to 1.05)	544 per 1,000	**22 fewer per 1,000** (71 fewer to 27 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25
Pneumonia (including respiratory tract infections, final values, lower is better)	1839 (2 RCTs) Mean follow-up: 20 weeks	⊕◯◯◯ Very low[b,c,h]	**RR 0.69** (0.29 to 1.66)	14 per 1,000	**4 fewer per 1,000** (10 fewer to 9 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to population indirectness (8% of participants had been treated with oral xanthines or leukotriene modifiers prior to study)

b. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

c. Downgraded by one increment due to concerns arising from deviations from the intended intervention (adherence monitoring not included)

d. Downgraded by one increment due to population indirectness (9% of participants had been treated with leukotriene modifiers prior to study)

e. Downgraded by one increment due to the 95%CI overlapping one MID (0.8-1.25)

f. Downgraded by one increment due to population indirectness (in primary study 8% of participants had been treated with oral xanthines or leukotriene modifiers prior to study, not reported in paper informing this analysis)

g. Downgraded by two increments due to inadequate power (not estimable)

h. Downgraded by one increment due to population indirectness (9% of participants had been treated with leukotriene modifiers prior to study) and one due to outcome indirectness (assessed respiratory tract infections, not pneumonia as specified)

Table 16 Clinical evidence summary: Regular moderate/high dose ICS with SABA prn vs regular low/moderate dose ICS plus montelukast with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS plus montelukast	Risk difference with regular ICS	
Severe asthma exacerbations at 3-5 months (final values, lower is better)	1029 (2 RCTs) Follow-up: 12 weeks	⊕⊕◯◯ Low[a,b]	**RR 1.58** (0.83 to 3.02)	27 per 1,000	**16 more per 1,000** (5 fewer to 55 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS plus montelukast	Risk difference with regular ICS	
Severe exacerbation rate (final values, lower is better)	140 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[a,b]	**Rate ratio 0.45** (0.20 to 0.99)	-	- Clinically important benefit of ICS plus montelukast	MID=0.8-1.25
Quality of life (Asthma quality of life questionnaire, scale range: 1-7, final values, higher is better)	52 (1 RCT) Follow-up: 12 weeks	⊕◯◯◯ Very low[b,c]	-	The mean AQLQ score was **5.6**	MD **0.24 lower** (0.77 lower to 0.29 higher) No clinical difference	MID=0.5 (established MID)
Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)	140 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[d]	-	The mean ACT score was **19.4**	MD **0.5 lower** (2.04 lower to 1.04 higher) No clinical difference	MID=3 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS plus montelukast	Risk difference with regular ICS	
Reliever/rescue medication use (puffs per day, change scores, lower is better)	889 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[e]	-	The mean change in reliever use was **-0.63 puffs per day**	MD **0.19 higher** (0.03 higher to 0.35 higher) No clinical difference	MID=0.81 puffs per day (established MID)
Lung function (FEV_1, % of predicted, change scores, higher is better)	140 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[a,b]	-	The mean change in FEV_1 was **1.97% of predicted**	MD **2.94 lower** (6.23 lower to 0.35 higher) No clinical difference	MID=4.96 (calculated as final SD/2)
Lung function (PEF, L/minute, change scores, higher is better)	941 (2 RCTs) Follow-up: 12 weeks	⊕⊕⊕◯ Moderate[e]	-	The mean change in PEF was **32.6 L/min**	MD **3 lower** (12.02 lower to 6.01 higher) No clinical difference	MID=18.79 (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS plus montelukast	Risk difference with regular ICS	
Adverse events (final values, lower is better)	964 (2 RCTs) Follow-up: 12 weeks	⨁⨁◯◯ Low[b,e]	**RR 1.12** (0.97 to 1.29)	400 per 1,000	**48 more per 1,000** (12 fewer to 116 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to some concerns of risk of bias (unclear if missing data and/or if ITT or PP analyses used; no pre-specified analyses in a protocol)

b. Downgraded by one increment due to the 95%CI overlapping one MID

c. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended interventions (adherence to montelukast and placebo treatments was 77% and 84%, respectively) and missing outcome data (paired data reported only)

d. Downgrade by two increments due to the being at high risk of bias (self-reported outcome and open-label study; unclear if missing data and/or if ITT or PP analyses used; no pre-specification of analyses in a protocol)

e. Downgraded by one increment due to concerns arising from a lack of clarity surrounding the randomisation process (method not reported) and deviations from the intended interventions (adherence to interventions not reported)

Children aged 5-11 years

Table 17: Clinical evidence summary: regular paediatric moderate/high dose ICS/LABA with SABA prn vs regular paediatric moderate/high dose ICS with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Severe asthma exacerbations at 3-5 months (final values, lower is better)	779 (3 RCTs) Follow-up: 12 weeks	⊕⊕◯◯ Low[a,b]	**RR 0.70** (0.40 to 1.23)	64 per 1,000	**19 fewer per 1,000** (38 fewer to 15 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Severe asthma exacerbations at ≥6 months (final values, lower is better)	407 (3 RCTs) Mean follow-up: 42 weeks	⊕⊕◯◯ Low[b,c]	**RR 1.72** (1.12 to 2.63)	132 per 1,000	**95 more per 1,000** (16 more to 215 more) Clinically important benefit for ICS	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Severe exacerbation rate (events per person year, lower is better)	223 (1 RCT) Follow-up: 52 weeks	⊕⊕◯◯ Low[b,c]	**Rate ratio 1.47** (0.95 to 2.29)	-	**-**	MID=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Mortality (final values, lower is better)	273 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[a,d]	**RD 0.00** (-0.02 to 0.02)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer) No clinical difference	MID clinical importance=1 per 1000, imprecision=0.8-1.25
Quality of life (PAQLQ, scale range: 1-7, change scores, lower is better)	188 (2 RCTs) Mean follow-up: 37 weeks	⊕⊕◯◯ Low[e]	-	The mean change in PAQLQ was **0.82**	MD **0.14 higher** (0.15 lower to 0.43 higher) No clinical difference	MID=0.5 (established MID)
Hospital admissions (final values, lower is better)	212 (2 RCTs) Mean follow-up: 37 weeks	⊕◯◯◯ Very low[f,g,h]	**OR 0.42** (0.13 to 1.36)	95 per 1,000	**53 fewer per 1,000** (81 fewer to 30 more) Clinically important benefit for ICS/LABA	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Reliever/rescue medication use (puffs per day, mixed values, lower is better)	496 (2 RCTs) Mean follow-up: 32 weeks	⊕⊕⊕◯ Moderate[c]	-	The mean reliever medication use was **0.74** puffs per day	MD **0.01 puffs per day higher** (0.1 lower to 0.11 higher) No clinical difference	MID=0.81 (established MID)
Reliever/rescue medication use (reliever-free days, % of days, final values, higher is better)	223 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[c]	-	The mean number of reliever-free days was **64.0** %	MD **3.5 % higher** (15.61 lower to 22.61 higher) No clinical difference	MID= 36.36 (calculated as final SD/2)
Lung function (PEF, % of predicted, final values, higher is better)	158 (1 RCT) Follow-up: 26 weeks	⊕⊕⊕◯ Moderate[i]	-	The mean PEF was **94.1** % of predicted	MD **2.2 % higher** (2.74 lower to 7.14 higher) No clinical difference	MID=7.88 (calculated as baseline SD/2)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Lung function (PEF, L/min, mixed values, higher is better)	747 (3 RCTs) Mean follow-up: 25 weeks	⊕⊕⊕◯ Moderate[c]	-	The mean PEF was **238** L/min	MD **5.35 L/min higher** (2.3 higher to 8.39 higher) No clinical difference	MID=18.79 L/min (literature MID)
Lung function (FEV_1, % of predicted, mixed values, higher is better)	179 (2 RCTs) Mean follow-up: 37 weeks	⊕◯◯◯ Very low[b,g,i]	-	The mean FEV_1 was **101.5** % of predicted	MD **6.38 % higher** (8.15 lower to 20.91 higher) No clinical difference	MID=8.3 (calculated as baseline SD/2)
Adverse events (final values, lower is better)	2010 (8 RCTs) Mean follow-up: 25 weeks	⊕⊕⊕◯ Moderate[j]	**RR 1.08** (0.98 to 1.19)	430 per 1,000	**34 more per 1,000** (9 fewer to 82 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS	Risk difference with regular ICS/LABA	
Pneumonia (including lower respiratory tract infections, final values, lower is better)	612 (3 RCTs) Mean follow-up: 30 weeks	⊕⊕⊕◯ Moderate[k]	RD 0.00 (-0.02 to 0.02)	11 per 1,000	**0 fewer per 1,000** (20 fewer to 20 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25
Adrenal insufficiency (number of participants with morning cortisol <400 nmol/L, final values, lower is better)	96 (1 RCT) Follow-up: 52 weeks	⊕◯◯◯ Very low[c,h]	**RR 0.25** (0.03 to 2.30)	73 per 1,000	**55 fewer per 1,000** (71 fewer to 95 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to concerns arising from deviations from the intended interventions (adherence not reported) and selection of the reported result (inadequate detail of pre-specified analysis)

b. Downgraded by one increment due to the 95%CI overlapping one MID

c. Downgraded by one increment due to concerns arising from deviations from the intended interventions (adherence not reported)

d. Downgraded by one increment based on inadequate sample size

e. Downgraded by two increments due to concerns arising from deviations from the intended interventions (adherence not reported and potential concomitant medication administration), measurement of the outcome (open-label study design with subjective outcome measure) and selection of the reported result (inadequate detail of pre-specified analysis)

f. Downgraded by two increments due to concerns arising from deviations from the intended interventions (adherence not reported and potential concomitant medication administration) and selection of the reported result (inadequate detail of pre-specified analysis)

g. Downgraded by two increments due to substantial heterogeneity

h. Downgraded by two increments due to the 95%CI overlapping both MIDs

i. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)

j. Downgraded by one increment due to concerns arising from various elements of the Risk of Bias tool (randomisation method not reported, adherence not reported, inadequate detail of pre-specified analyses)

k. Downgraded by one increment due to concerns arising from the randomisation process (method not reported) in the majority of the evidence

Table 18: Clinical evidence summary: ICS/formoterol MART vs regular paediatric moderate/high dose ICS/LABA with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS/LABA with SABA prn	Risk difference with ICS/form MART	
Severe asthma exacerbations at ≥6 months (final values, lower is better)	235 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	**RR 0.28** (0.14 to 0.53)	308 per 1,000	**222 fewer per 1,000** (265 fewer to 145 fewer) Clinically important benefit of MART	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Severe exacerbation rate (events per person year, lower is better)	235 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	**Rate ratio 4.77** (2.49 to 9.14)	-	-	MID=0.8-1.25
Reliever/rescue medication use (puffs per day, final values, lower is better	235 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean reliever medication use was **0.76** puffs per day	MD **0.18 puffs per day lower** (0.35 lower to 0.01 lower) No clinical difference	MID=0.81 puffs per day (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS/LABA with SABA prn	Risk difference with ICS/form MART	
Reliever/rescue medication use (reliever-free days, % of days, final values, higher is better)	235 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean number of reliever-free days was **67.5** %	MD **1.9 % higher** (3.36 lower to 7.16 higher) No clinical difference	MID=10.29 (calculated as final SD/2)
Lung function (PEF, L/min, final values, higher is better)	235 (1 RCT) Follow-up: 52 weeks	⊕⊕◯◯ Low[a,b]	-	The mean PEF was **242** L/min	MD **13 L/min higher** (7.72 lower to 33.72 higher) No clinical difference	MID=18.79 L/min (established MID)
Adverse events (final values, lower is better)	235 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	**RR 0.12** (0.03 to 0.53)	137 per 1,000	**120 fewer per 1,000** (133 fewer to 64 fewer) Clinically important benefit of MART	MID clinical importance=100 per 1000, imprecision=0.8-1.25
Pneumonia (final values, lower is better)	235 (1 RCT) Follow-up: 52 weeks	⊕◯◯◯ Very low[a,c]	**OR 0.13** (0.01 to 2.14)	17 per 1,000	**15 fewer per 1,000** (17 fewer to 19 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS/LABA with SABA prn	Risk difference with ICS/form MART	
Adrenal insufficiency (number of participants with morning cortisol <400 nmol/L, final values, lower is better)	106 (1 RCT) Follow-up: 52 weeks	⊕◯◯◯ Very low[a,c]	**RR 2.16** (0.20 to 23.07)	18 per 1,000	**21 more per 1,000** (15 fewer to 401 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to concerns arising from deviations from the intended interventions (adherence not reported)

b. Downgraded by one increment due to the 95%CI overlapping one MID threshold

c. Downgraded by two increments due to the 95%CI overlapping both MIDs

Table 19: Clinical evidence summary: ICS/formoterol MART vs regular paediatric moderate/high dose ICS with SABA prn

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS with SABA prn	Risk difference with ICS/form MART	
Severe asthma exacerbations at ≥6 months (final values, lower is better)	224 (1 RCT) Follow-up: 52 weeks	⊕⊕◯◯ Low[a,b]	**RR 0.43** (0.21 to 0.87)	198 per 1,000	**113 fewer per 1,000** (157 fewer to 26 fewer) Clinically important benefit of MART	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS with SABA prn	Risk difference with ICS/form MART	
Severe exacerbation rate (events per person year, lower is better)	224 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	**Rate ratio 3.24** (1.63 to 6.42)	-	**-**	MID =0.8-1.25
Reliever/rescue medication use (puffs per day, final values, lower is better)	224 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean reliever use was **0.74** puffs per day	MD **0.16 puffs per day lower** (0.35 lower to 0.03 higher) No clinical difference	MID=0.81 puffs per day (established MID)
Reliever/rescue medication use (reliever-free days, % of days, final values, higher is better)	224 (1 RCT) Follow-up: 52 weeks	⊕⊕⊕◯ Moderate[a]	-	The mean number of reliever-free days was **64.0** %	MD **5.4 % higher** (1.38 lower to 12.18 higher) No clinical difference	MID=12.93 (calculated as final SD/2)
Lung function (PEF, L/min, final values, higher is better)	224 (1 RCT) Follow-up: 52 weeks	⊕⊕◯◯ Low[a,b]	-	The mean PEF was **238** L/min	MD **17 L/min higher** (6.4 higher to 27.6 higher) No clinical difference	MID=18.79 L/min (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS with SABA prn	Risk difference with ICS/form MART	
Adverse events (final values, lower is better)	224 (1 RCT) Follow-up: 52 weeks	⊕◯◯◯ Very low[a,c]	**RR 0.36** (0.07 to 1.81)	47 per 1,000	**30 fewer per 1,000** (44 fewer to 38 more) No clinical differenc	MID clinical importance=100 per 1000, imprecision=0.8-1.25
Pneumonia (final values, lower is better)	201 (1 RCT) Follow-up: 52 weeks	⊕⊕◯◯ Low[a,d]	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer) No clinical differenc	MID clinical importance=100 per 1000, imprecision=0.8-1.25
Adrenal insufficiency (number of participants with morning cortisol <400 nmol/L, final values, lower is better)	92 (1 RCT) Follow-up: 52 weeks	⊕◯◯◯ Very low[a,c]	**RR 0.54** (0.09 to 3.06)	73 per 1,000	**34 fewer per 1,000** (67 fewer to 151 more) No clinical differenc	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to concerns arising from deviations from the intended interventions (adherence not reported)

b. Downgraded by one increment due to the 95%CI overlapping one MID

c. Downgraded by two increments due to the 95%CI overlapping both MIDs

d. Downgraded by one increment due to an inadequate sample size to appropriately power the analysis

Table 20: Clinical evidence summary: regular paediatric moderate/high dose ICS vs regular paediatric moderate dose ICS with montelukast

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS with montelukast	Risk difference with Regular ICS	
Severe asthma exacerbations at ≥6 months (final values, lower is better)	23 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[a,b,c]	**RR 1.09** (0.08 to 15.41)	83 per 1,000	**8 more per 1,000** (77 fewer to 1,201 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Quality of life (Paediatric Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)	22 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[b,d,e]	-	The mean change in PAQLQ score was **1.84**	MD **0.55 lower** (1.56 lower to 0.46 higher) Clinically important benefit for ICS +Montelukast	MID=0.5 (established MID)
Hospital admissions (final values, lower is better)	37 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[b,d,f]	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS with montelukast	Risk difference with Regular ICS	
Lung function (FEV_1, % of predicted, change scores, higher is better)	17 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[b,c,d]	-	The mean change in FEV_1 was **4.55** % of predicted	MD **4.43 % of predicted lower** (18.03 lower to 9.17 higher) No clinical difference	MID=7.14 (calculated as final SD/2)
Adverse events (final values, lower is better)	40 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[a,b,e]	**RR 1.04** (0.83 to 1.32)	857 per 1,000	**34 more per 1,000** (146 fewer to 274 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to concerns arising from missing outcome data (missing data rate greater than event rate)

b. Downgraded by one increment due to population indirectness (age variance overlaps upper limit of age strata)

c. Downgraded by two increments due to the 95%CI overlapping both MIDs

d. Downgraded by two increments due to concerns arising from missing outcome data (missing data rate greater than event rate, and disproportionate rate of missingness between arms)

e. Downgraded by one increment due to the 95%CI overlapping one MID

f. Downgraded by two increments due to inadequate sample size to appropriately power the analysis

Table 21: Clinical evidence summary: regular paediatric moderate/high dose ICS/LABA vs regular paediatric moderate dose ICS with montelukast

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS with montelukast	Risk difference with regular ICS/LABA	
Severe asthma exacerbations at ≥6 months (final values, lower is better)	27 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[a,b,c]	**RR 4.00** (0.54 to 29.80)	83 per 1,000	**250 more per 1,000** (38 fewer to 2,400 more) Clinically important benefit for ICS + Montelukast	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Quality of life (Paediatric Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)	27 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[b,c,d]	-	The mean change in PAQLQ score was **1.84**	MD **0.74 lower** (2.07 lower to 0.59 higher) Clinically important benefit for ICS + Montelukast	MID=0.5 (established MID)
Hospital admissions (final values, lower is better)	36 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[b,d,e]	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular ICS with montelukast	Risk difference with regular ICS/LABA	
Lung function (FEV_1, % of predicted, change scores, higher is better)	22 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[b,d,f]	-	The mean change in FEV_1 was **4.55**	MD **10.99 higher** (3.92 lower to 25.9 higher) Clinically important benefit for ICS/LABA	MID=8.9 (calculated as final SD/2)
Adverse events (final values, lower is better)	44 (1 RCT) Follow-up: 48 weeks	⊕◯◯◯ Very low[a,b,f]	**RR 0.91** (0.69 to 1.20)	857 per 1,000	**77 fewer per 1,000** (266 fewer to 171 more) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by one increment due to concerns arising from missing outcome data (missing data rate greater than event rate)

b. Downgraded by one increment due to population indirectness (age variance overlaps upper limit of age strata)

c. Downgraded by two increments due to the 95%CI overlapping both MIDs

d. Downgraded by two increments due to concerns arising from missing outcome data (missing data rate greater than event rate, and disproportionate rate of missingness between arms)

e. Downgraded by two increments due to inadequate sample size to appropriately power the analysis

f. Downgraded by one increment due to the 95%CI overlapping one MID

Children under 5 years

Table 22: Clinical evidence summary: regular ICS vs as-needed ICS/SABA

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with as-needed ICS/SABA	Risk difference with Regular ICS	
Severe asthma exacerbations at 3-5 months (final values, lower is better)	499 (1 RCT) Follow-up: 16 weeks	⊕◯◯◯ Very low[a,b]	**RR 0.68** (0.49 to 0.95)	276 per 1,000	**88 fewer per 1,000** (141 fewer to 14 fewer) Clinically important benefit for ICS	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Hospital admissions at 3-5 months (final values, lower is better)	499 (1 RCT) Follow-up: 16 weeks	⊕◯◯◯ Very low[a,c]	**OR 0.14** (0.00 to 6.85)	4 per 1,000	**3 fewer per 1,000** (4 fewer to 23 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Pneumonia (final values, lower is better)	499 (1 RCT) Follow-up: 16 weeks	⊕◯◯◯ Very low[a,c]	**Peto OR 7.42** (0.15 to 373.89)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by two increments due to concerns arising from the randomisation process and missing outcome data

b. Downgraded by one increment due to the 95%CI overlapping the lower MID (0.8-1.25)

c. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

Table 23: Clinical evidence summary: regular ICS vs regular montelukast

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular montelukast	Risk difference with Regular ICS	
Severe asthma exacerbations at 3-5 months (final values, lower is better)	505 (1 RCT) Follow-up: 16 weeks	⊕⊕◯◯ Low[a]	**RR 0.56** (0.41 to 0.76)	340 per 1,000	**150 fewer per 1,000** (201 fewer to 82 fewer) Clinically important benefit for ICS	MID (clinical importance) =30 per 1,000, (imprecision)=0.8-1.25
Severe asthma exacerbations at >6 months (final values, lower is better)	202 (1 RCT) Follow-up: 52 weeks	⊕◯◯◯ Very low[b,c]	**RR 0.59** (0.38 to 0.92)	371 per 1,000	**152 fewer per 1,000** (230 fewer to 30 fewer) Clinically important benefit for ICS	MID (clinical importance) =30 per 1,000, (imprecision)=0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular montelukast	Risk difference with Regular ICS	
Mortality (final values, lower is better)	202 (1 RCT) Follow-up: 52 weeks	⊕◯◯◯ Very low[b,d]	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer) No clinical difference	MID (clinical importance) =1 per 1,000, (imprecision)=0.8-1.25
Hospital admissions at 3-5 months (final values, lower is better)	505 (1 RCT) Follow-up: 16 weeks	⊕⊕◯◯ Low[a]	**OR 0.14** (0.03 to 0.68)	23 per 1,000	**20 fewer per 1,000** (23 fewer to 7 fewer) No clinical difference	MID (clinical importance) =30 per 1,000, (imprecision)=0.8-1.25
Reliever/rescue medication use (puffs per day, change scores, lower is better)	201 (1 RCT) Follow-up: 12 weeks	⊕⊕◯◯ Low[b]	-	The mean change in reliever use was **-0.72** puffs per day	MD **0.03 puffs per day higher** (0.28 lower to 0.34 higher) No clinical difference	MID=0.81 puffs per day (established MID)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular montelukast	Risk difference with Regular ICS	
Lung function (PEF, L/min, change scores, higher is better)	146 (1 RCT) Follow-up: 12 weeks	⨁⨁◯◯ Low[b]	-	The mean change in PEF was **14** L/min	MD **7.1 L/min higher** (0.43 lower to 14.63 higher) No clinical difference	MID=18.79 L/min (established MID)
Adverse events (final values, lower is better)	202 (1 RCT) Follow-up: 52 weeks	⨁⨁◯◯ Low[b]	**RR 0.97** (0.85 to 1.11)	825 per 1,000	**25 fewer per 1,000** (124 fewer to 91 more) No clinical difference	MID (clinical importance) =100 per 1,000, (imprecision)=0.8-1.25
Pneumonia (final values, lower is better)	707 (2 RCTs) Mean follow-up: 34 weeks	⨁◯◯◯ Very low[b,e]	**OR 0.77** (0.23 to 2.57)	17 per 1,000	**4 fewer per 1,000** (13 fewer to 26 more) No clinical difference	MID (clinical importance) =100 per 1,000, (imprecision)=0.8-1.25

a. Downgraded by two increments due to concerns arising from the randomisation process and missing outcome data

b. Downgraded by two increments due to concerns arising from the randomisation process, deviations from the intended interventions and missing outcome data

c. Downgraded by one increment due to the 95%CI overlapping one MID

d. Downgraded by two increments due to inadequate sample size (power <80%)

e. Downgraded by two increments due to the 95%CI overlapping both MIDs

Table 24: Clinical evidence summary: as-needed ICS/SABA vs regular montelukast

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with regular montelukast	Risk difference with As-needed ICS/SABA	
Severe asthma exacerbations at 3-5 months (final values, lower is better)	506 (1 RCT) Follow-up: 16 weeks	⊕◯◯◯ Very low[a,b]	**RR 0.81** (0.62 to 1.06)	340 per 1,000	**65 fewer per 1,000** (129 fewer to 20 more) Clinically important benefit for ICS/SABA	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Hospital admissions at 3-5 months (final values, lower is better)	506 (1 RCT) Follow-up: 16 weeks	⊕◯◯◯ Very low[a,b]	**RR 0.17** (0.02 to 1.41)	23 per 1,000	**19 fewer per 1,000** (23 fewer to 10 more) No clinical difference	MID clinical importance=30 per 1000, imprecision=0.8-1.25
Pneumonia (final values, lower is better)	506 (1 RCT) Follow-up: 16 weeks	⊕◯◯◯ Very low[a,c]	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer) No clinical difference	MID clinical importance=100 per 1000, imprecision=0.8-1.25

a. Downgraded by two increments due to concerns arising from the randomisation process and missing outcome data

b. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

c. Downgraded by two increments due to inadequate sample size (power <80%)

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

Six health economic studies (seven papers) with relevant comparisons were included in this review:

- 1 comparing ICS low dose versus regular low dose ICS/LABA versus ICS low dose plus regular montelukast in children (Lenney 2013)(Lenney et al., 2013)
- 1 comparing: moderate dose ICS + LTRA versus moderate dose ICS/LABA in adults (published in two papers: Price 2011/Wilson 2010)(Price et al., 2011, Wilson, et al., 2010)
- 1 comparing: Low dose ICS versus low dose ICS+LABA versus low dose ICS+ LTRA versus moderate dose ICS in adults (NICE 2017, NG80)(National Institute for Health and Care Excellence, 2017)
- 1 comparing: MART versus ICS/LABA or ICS as maintenance and SABA as reliever in adults (Wickstrom 2009)(Wickstrom, et al., 2009)
- 2 comparing ICS/LABA/LAMA versus ICS/LABA in adults (Mangia 2021 and Mtibaa 2021)(Mangia, et al., 2021, Mtibaa, et al., 2021)

These are summarised in the health economic evidence profiles below (Table 3, Table 4, Table 5, Table 6, Table 7) and the health economic evidence tables in Appendix H.

1.1.7.2 Excluded studies

Eight economic studies relating to this review question were identified but were excluded due to limited applicability or due to a combination of limited applicability and methodological limitations and the availability of more applicable evidence. (Main, et al., 2008),(Tamminen, et al., 2008),(Miller, et al., 2008),(Miller, et al., 2007),(Buendia, et al., 2021), (Buendia, et al., 2021) (Buendia, et al., 2022), (Buendia, et al., 2022),(Antonio Buendia, et al., 2023)These are listed in Appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

Table 3: Health economic evidence profile: ICS low dose vs regular low dose ICS/LABA vs ICS low dose plus regular montelukast in children

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Lenney (2013)(Lenney et al., 2013)(UK)	Partially applicable [a]	Potentially serious limitations[b]	• Within-RCT analysis (MASCOT RCT / Lenney 2013)(Lenney et al., 2013) • Cost-utility analysis (QALYs) • Population: Children aged 6–14 years with asthma requiring frequent short-acting beta-2 agonist relief, with symptoms of asthma resulting in nocturnal wakening and/or asthma that has interfered with usual activities. • Comparators: 1.Regular low-dose ICS 2.Regular low-dose ICS/LABA combination 3.Regular low-dose ICS plus regular montelukast Time horizon: 48 weeks	Incremental (2−1): £314.05 Incremental (3−1): £303.24 Incremental (3-2): saves £10.81[c]	Incremental (2−1): 0.03 Incremental (3−1): 0.04 Incremental (3-2): 0.02	2 is dominated by 3 (less costly and more effective) Intervention 3 costs £6,827 per QALY gained compared to intervention 1	Probability Intervention 2 is cost effective (£30K threshold, compared with intervention 1): 60% Probability Intervention 3 is cost effective (£30K threshold, compared with intervention 1): 80% Bootstrapping Missing data handled by using different imputation assumptions informed by data collected on reasons for missing data.

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial, MASCOT = Management of Asthma in School age Children On Therapy, CUA = Cost-utility analysis, PAQLQ(S) = Standardised Paediatric Asthma Quality of Life Questionnaire (PAQLQ(S)), OTC = Over the counter, BNF = British

National Formulary, PSSRU = Personal Social Services Research Unit, NIHR = National Institute for Health and Care Research, MRCN = NIHR Medicines for Children Research Network, HTA = Health Technology Assessment. ICS = Inhaled corticosteroid, LABA = Long-acting beta2 agonist, LTRA = Leukotriene receptor antagonist.

(a) The trial enrolled children older than 12 which makes it not fully aligned with the clinical protocol (5 – 12).

(b) The study suffered from high attrition and only a limited number of participants could be successfully randomised. Short time horizon may not adequately reflect long term outcomes and effects. unclear if utility weights were derived from PAQLQ(s)n using the preference of the UK general population. Treatment effects and outcomes based on the singular study RCT, may not reflect full scope of evidence. Patient diary used as sole source of resource use, this is prone to recall bias, and potential conflict of interest

(c) 2009-2010 UK pounds costs. Cost components incorporated: All relevant healthcare costs included, such as prescribed inhalers and prescribed medicine cost, over the counter medicine cost, GP costs, walk-in costs, specialist doctor cost, A&E visit costs and hospital admission costs.

Table 4: Health economic evidence profile: ICS + LTRA versus ICS/LABA in adults

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Price 2011(Price et al., 2011), also published in Wison 2010(Wilson et al., 2010) (UK)	Partially applicable [a]	Potentially serious limitations[b]	• Within-RCT analysis (ELEVATE RCT, Price 2011)(Price et al., 2011) • Cost-utility analysis (QALYs) • Population: Patients aged 12-80 years with diagnosed asthma who had received inhaled steroid for at least the last 12 weeks and had not received a long-acting β2-agonist or leukotriene antagonist in the previous 12 weeks. • Comparators: 1. Moderate dose ICS/LABA 2. Moderate dose ICS + LTRA Follow up: 2 years	**Total NHS costs (mean per patient):** £113[c]	**QALYs (mean per patient):** 0.053 Adjusted[d]: 0.009 **MiniAQLQ (mean per patient):** 0.037 Adjusted[c]: 0.034	£11,919 per QALY gained (using adjusted QALYs)	Probability ICS+LTRA cost effective (£20K/£30K threshold): 50%/53%

Abbreviations: CUA: cost-utility analysis; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Not all comparators from protocol included (no MART) and it is step up from low dose ICS + SABA rather than ICS+LABA. Montelukast or zafirlukast used in study.

(b) 2005 NHS unit costs may not reflect current NHS costs. Montelukast is now out of patent which reduces the price significantly since the date of study. This would increase the cost effectiveness of ICS+LTRA and possibly see it as cost-saving compared to ICS+LABA and therefore dominant. This is one of 2 RCTs comparing ICS+LABA to ICTS+LTRA and therefore may not reflect the full body on clinical evidence. The pragmatic nature of the RCT on which the evaluation is based may not reflect the true treatment effect sizes.
(c) 2005 UK pounds. Cost components incorporated: Prescribed medication and devices, primary and secondary care activity.
(d) Including imputed data and adjusted for baseline values.

Table 5: Health economic evidence profile: Low dose ICS versus low dose ICS/LABA versus low dose ICS+ LTRA versus moderate dose ICS in adults

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost</th><th>Incremental effects</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr><td>NICE 2017 (NG80)(National Institute for Health and Care Excellence, 2017)
(UK)</td><td>Partially applicable[a]</td><td>Potentially serious limitations[b]</td><td>• Probabilistic model based on meta-analysis of RCTs
• Cost-utility analysis (QALYs)
• Population: adults over 16 years of age, whose asthma has remained uncontrolled using routine low dose ICS and SABA for symptom relief.
• Comparators[c]:
1. Low dose ICS
2. Low dose ICS/LABA
3. Low dose ICS + LTRA
4. Moderate dose ICS
Time horizon: lifetime</td><td colspan="4">Full incremental analysis[d]:
<table><tr><td>Intervention</td><td>QALYs</td><td>Costs[e]</td><td>ICER</td><td>Probability CE @£20K</td></tr><tr><td>ICS+LTRA</td><td>16.222</td><td>£3,923</td><td>-</td><td>71%</td></tr><tr><td>Moderate ICS</td><td>16.221</td><td>£4,653</td><td>Dominated</td><td>13%</td></tr><tr><td>ICS+LABA</td><td>16.234</td><td>£4,639</td><td>£56,977</td><td>12%</td></tr><tr><td>Low dose ICS</td><td>16.113</td><td>£5,068</td><td>Dominated</td><td>3%</td></tr></table>A number of sensitivity analyses conducted, none changed conclusion of base case, ICS+LTRA remained cost effective option.</td></tr>
</table>

Abbreviations: CUA: cost-utility analysis; ICER: incremental cost-effectiveness ratio; ICS: inhaled corticosteroids; LABA: long acting beta agonists; LTRA: leukotriene receptor antagonists; QALY: quality-adjusted life years; RCT: randomised controlled trial; SABA: short acting beta agonists.
(a) Comparators not directly relevant to review question. Not all comparators from protocol included (no MART) and it is step up from low dose ICS + SABA rather than ICS/LABA.
(b) 2016 NHS unit costs may not reflect current NHS costs. Direct evidence only existed against ICS/LABA, no direct evidence between low dose ICS, moderate dose ICS and ICS + LTRA. Most of the RCT evidence used in model is not included in clinical review due to incorrect intervention/comparator/study population or outcomes that are not extractable (Bjermer 2003, Greening 1994 and O'Byrne 2001). Heavy reliance on a single pragmatic RCT (Price 2011) for several inputs including baseline exacerbation rate for ICS+LABA, disutility of starting on low dose ICS+LTRA, resource use, drug adherence and switching. Model assumptions biased against ICS+LTRA. Disutility for exacerbating based on single study and considered high. Non-exacerbation-related healthcare costs remained high for ICS+LTRA throughout the model

(c) All of the strategies included assume the use of SABAs for short-term symptom relief.
(d) Estimates are ranked from the least costly to the most costly. Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.
(e) 2016 UK pounds. Cost components incorporated: Drug costs and healthcare utilisation (including exacerbation and non-exacerbation HC use)

Table 6: Health economic evidence profile: MART versus ICS/LABA as maintenance and SABA as reliever in adults

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Wickstrom 2009(Wickstrom et al., 2009) (Denmark)	Partially applicable [a]	Potentially serious limitations[b]	• Within-RCT analysis (multiple RCTs) • Cost-effectiveness analysis (severe exacerbations) • Population: Adults and children over 8 years of age with persistent asthma. Mean age: 36-45. At baseline participants had either ICS alone or with LABA as maintenance therapy. • Comparators:[c] **First treatment change**: Rabe 2006(Rabe et al., 2006): 1. ICS/LABA (low dose) 2. MART (ICS/LABA low dose) O'Byrne 2005: 1. ICS/LABA (low dose) 2. MART (ICS/LABA low dose) **Subsequent treatment change**: Kuna 2007(Kuna et al., 2007):[d] 1. ICS/LABA (moderate dose)	**Total costs (mean per patient):**[e] **First treatment change:** Rabe 2006: £8 O'Byrne 2005: Saves £19 **Subsequent treatment change:** Kuna 2007: Saves £184 to £188 Bousquet 2007: £56 O'Byrne 2005:	**Severe exacerbations per patient per year:** **First treatment change:** Rabe 2006: 0.10 fewer O'Byrne 2005: 0.21 fewer **Subsequent treatment change:** Kuna 2007: 0.08 to 0.14 fewer Bousquet 2007: 0.06 fewer O'Byrne 2005: 0.16 fewer	Kuna 2007 and O'Byrne 2005: Intervention 2 dominated intervention 1 by Reducing exacerbations and reducing costs to the health service. Rabe 2006: Intervention 2 costs an additional £82 per exacerbation avoided. Bousquet 2007: Intervention 2 costs an additional £868 per exacerbation avoided. Vogelmeir 2005: Intervention 2 costs an additional £458 per exacerbation avoided.	Univariate sensitivity analyses conducted, but none changed the results of the base case analysis.

			2. MART (ICS/LABA, low dose) Bousquet 2007: 1. ICS/LABA (high dose) 2. MART (ICS/LABA, moderate dose) O'Byrne 2005(O'Byrne et al., 2005): 1. ICS/LABA (moderate dose) 2. MART (ICS/LABA, low dose) Vogelmeier 2005(Vogelmeier et al., 2005): 1. ICS/LABA (high dose 2. MART (ICS/LABA, moderate dose) Follow up: 1 year	saves £12 Vogelmeir 2005: £18	Vogelmeir 2005: 0.04 fewer		

Abbreviations: CEA: cost-effectiveness analysis; ICS: inhaled corticosteroids; LABA; long-acting beta-agonist; MART: maintenance and reliever therapy

(a) Resource use for each trial was pooled across multiple countries rather than just the UK. In addition, Danish unit costs were applied, making the results less applicable to UK NHS perspective. EQ-5D not included as an outcome, though reported outcomes would suggest it is at least not lower in the MART group.

(b) Time horizon of only 1 year may not be capturing the full effect of interventions. Limited sensitivity analyses conducted. Unit costs from 2007, may not reflect current NHS costs. Rabe 2006 and O'Byrne 2005 are indirect evidence for first treatment change as all participants had received moderate dose ICS prior to trial entry. Potential conflict of interest.

(c) All intervention 1 had SABA as a reliever to be used as needed.

(d) There were two ICS/LABA arms compared to MART. One with budesonide/formoterol and the other with salmetorol/fluticasone. Both presented here.

(e) 2007 Danish Krone presented here as 2007 UK Pounds converted using purchasing power parities. Cost components incorporated: asthma medication, hospitalisation, unplanned emergency visit, visit to GP, visit to pulmonologist.

Table 7: Health economic evidence profile: ICS/LABA/LAMA versus ICS/LABA in adults

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Mangia 2021(Mangia et al., 2021) (Italy)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic model based on clinical trials Two phase III studies, ARGON and IRIDIUM • Cost-utility analysis (QALYs) • Population: Adult patients with asthma aged 18 years and older who are	Incremental (1−2): £4,919	Incremental (1−2): 0.34 QALYs	1 vs 2: £14,601 per QALY gained 1 vs 3: £12,331 per QALY gained	Probability intervention 1 cost effective (£19.7K threshold): vs. 2: 65% vs. 3: 80% vs. 4: 100%

			inadequately controlled despite treatment with high-dose inhaled corticosteroids and LABAs. • Comparators: 1. ICS/LABA/LAMA: Indacaterol/ glycopyrronium/ Mometasone furoate 150/50/320 µg once daily. 2. ICS/LABA: Mometasone/ Indacaterol 150/320 µg, once daily 3. ICS/LABA:Salmeterol/Fluticasone 50/500 µg, twice daily 4. ICS/LABA plus LAMA: Salmeterol/fluticasone 50/500 µg, twice daily plus tiotropium 5 µg once daily • Time horizon: Lifetime	Incremental (1−3): £2,641 Incremental (1−4): saves £3,331 [(c)]	Incremental (1−3): 0.21 QALYs Incremental (1−4): 0.25 QALYs	1 vs 4: 1 dominates 4 (less costly and more effective) In addition, Intervention 4 is dominated by intervention 3 (less costly and more effective) and is not cost effective compared to intervention 2 (ICER >30K).	**Analysis of uncertainty:** Bootstrapping Missing data handled by using different imputation assumptions informed by data collected on reasons for missing data.
Mitibaa 2021(Mtiba a et al., 2021) (Canada)	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Decision analytical model – Markov Model • Cost-utility analysis (QALYs) • Population: Patients (aged ≥18 years) with a diagnosis of moderate-to-severe asthma not adequately controlled by a maintenance combination of a LABA and a moderate- or high-dose ICS. Comparators: • LABA/LAMA/ICS: Indacaterol/ glycopyrronium/	Incremental (1−2) saves £9627 Incremental (1−3) saves £1753[(f)]	Incremental (1−2) 0.31 QALYs Incremental (1−3) 0.29 QALYs	Intervention 1 dominates all other interventions (less costly and more effective).	Probability intervention 1 cost effective versus intervention 2/ intervention 3 (£20K threshold): ~40%/~90% **Analysis of uncertainty:** Scenario analysis conducted for intervention 1 versus intervention 3 comparison. Changes to discount rates, time horizon and discontinuation rate did not change the

			Mometasone furoate 150/50/160 µg once daily. • LABA/ICS: Salmeterol/Fluticasone 50/500 µg Twice daily • LABA/ICS+LAMA: Salmeterol/Fluticasone 50/500 µg Twice daily + Tiotropium 5 µg Once daily • Time horizon: Lifetime				conclusion of the base-case scenario.

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial, LABA = Long acting beta2 agonist, LAMA = Long-acting muscarinic antagonist, ICS = inhaled corticosteroid,

(a) Italian healthcare perspective, uses 3% discounted not 3.5%, also lack of clarity in where exactly QALYs are derived.

(b) Source of outcome data taken from only two clinical trials, may not reflect full scope of evidence. Baseline source of outcome unclear, sources of costs derived from Italian healthcare sources which may not be applicable to the NHS. Potential conflict of interest.

(c) 2021 Italian Euros converted to UK pounds (OECDPPP). Cost components incorporated: Pharmaceutical costs and exacerbation management costs.

(d) Canadian healthcare perspective. Uses 1.5% discounted not 3.5%. AQLQ mapped to EQ-5D for quality of life data

(e) Source of outcome data taken from only two clinical trials, may not reflect full scope of evidence. Costs sourced from Canadian health sources which may not be applicable to NHS. Potential conflict of interest.

(f) 2020 costs Canadian Dollars converted to UK pounds (OECDPPP). Cost components incorporated: Drug costs, healthcare resource use per exacerbation.

Table 8: Health economic evidence profile: MART versus ICS/LABA or ICS as maintenance and SABA as reliever

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
NICE 2024 (UK)	Directly applicable	Minor limitations	• Life-table model adjusted for asthma specific mortality. Costs and quality of life were attached to symptom status and to severe exacerbations. Three populations were explored using the same model with inputs and	Analysis 1: Incremental (2-1): £141 Analysis 2: Incremental (2-1): £16 Analysis 3: Incremental: (2-1): £22	Analysis 1: Incremental (2-1): 0.022 QALYs Analysis 2: Incremental (2-1): 0.003 QALYs Analysis 3:	Analysis 1: £6,382 (MART vs ICS/LABA) Analysis 2: £4,769 (ICS/LABA vs MART) Analysis 3: MART dominated (less costly and	Probabilistic and scenario analyses were conducted for the three populations. (see summary below for more detail)

			assumptions specific to each group: • Analysis 1, escalation to low-dose MART in adults with uncontrolled asthma (first escalation) • Analysis 2, escalation to moderate-dose MART in adults with uncontrolled asthma (subsequent escalation) • Analysis 3, escalation to low-dose MART in children with uncontrolled asthma • Cost-utility analysis (QALYs) • Population: • Analysis 1, Adults (age 40.7 years) • Analysis 2, adults (age 42.1 years)	(3-1): £174	Incremental: (2-1) -0.008 QALYs (3-1) -0.012 QALYs	more effective) both ICS/LABA and ICS	

			• Analysis 3, children (age 8 years) • Comparators – analysis 1: 1. Low/moderate-dose ICS/LABA +SABA prn 2. Low-dose MART • Comparators – analysis 2: 1. Moderate-dose MART 2. Moderate/high-dose ICS/LABA +SABA prn • Comparators – analysis 3: 1. Paediatric low-dose MART 2. Paediatric moderate-dose ICS + SABA prn 3. Paediatric low-dose ICS/LABA +SABA prn				

1.1.9 Economic model

A cost-utility analysis was developed to compare three scenarios of using MART as step-up treatment for people whose management treatment is not providing adequate control. Three comparisons were modelled:

1. Low-dose MART vs low/moderate-dose ICS/LABA + SABA PRN in adults

2. Moderate-dose MART vs moderate/high-dose ICS/LABA + SABA PRN in adults
3. Paediatric low-dose MART vs paediatric low-dose ICS/LABA + SABA PRN vs paediatric moderate-dose ICS + SABA PRN in children.

A life-table model was developed, adjusted for asthma-specific mortality over a 5-year time horizon, and the model utilised published data on symptom status, exacerbations, and reliever use to inform costs and quality of life for each treatment.

Data sources

- Cohort settings, severe exacerbations, symptom status and reliever use were informed by key studies identified in the clinical review for each of the analyses:
  - Atienza 2013,(Atienza et al., 2013) O'Byrne 2005,(O'Byrne et al., 2005) and Rabe 2006(Rabe et al., 2006) were used for analysis 1,
  - Bousquet 2007,(Bousquet et al., 2007) Patel 2013,(Patel et al., 2013) and Vogelmeier 2005(Vogelmeier et al., 2005) were used for analysis 2,
  - Bisgaard 2006(Bisgaard et al., 2006) was used for analysis 3.
- Costs of asthma management and monitoring were estimated using BNF,(BMJ Group and the Royal Pharmaceutical Society of Great Britain, Joint Formulary Committee, 2024) NHS National Collection Costs(NHS England, 2022) and PSSRU.(Jones, et al.)
- General population utility was informed using Kind et al. 1999(Kind, et al., 1998)
- The quality of life associated with controlled or uncontrolled asthma was calculated through a bespoke analysis of the Health Survey for England (HSE)(NHS Digital, 2019)
- Disutility associated with severe exacerbation was taken from Briggs et al. 2021(Briggs, et al., 2021)

Full details of the economic model are presented in XXX, and the main results of the analyses are summarised below. The base case analyses below are from an English NHS perspective. Analyses were also conducted from a Scottish NHS perspective, the results were similar to the English NHS perspective and are can be found in the full report.

When low-dose MART was compared with low/moderate-dose ICS/LABA + SABA PRN in adults who had uncontrolled asthma, low-dose MART was found to have a probabilistic ICER of £6,382 per QALY gained, consistent with the deterministic ICER. Moreover, the ICER remained below £20,000 per QALY gained for all scenario analyses. One scenario with a substantially different ICER was when the option to use different utility values based on symptom status was excluded. However, the ICER in this case remained below £20,000 per QALY gained.

Table 9: Probabilistic results, escalation to low-dose MART in adults

Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER	% cost-effective[(a)]
Low/moderate-dose ICS/LABA + SABA PRN	£1,327	3.549	-	-	-	1.00%

Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER	% cost-effective[(a)]
Low-dose MART	£1,468	3.571	£141	0.022	£6,382	99.00%

(a) Cost-effective at a threshold of £20,000 per QALY gained

In the comparison between moderate-dose MART and moderate/high-dose ICS/LABA + SABA PRN in adults, the MART regimen was found to have marginally lower costs and QALYs than ICS/LABA in the probabilistic base-case analysis, with ICS/LABA having an ICER of £4,769 per QALY gained compared with MART. The probabilistic analysis found that ICS/LABA had a 59.44% probability of being cost-effective compared with MART in the base-case, indicating some uncertainty in the analysis. The deterministic results were consistent with the probabilistic. Due to the very small incremental costs and incremental QALYs, the ICER varied more between each scenario analysis. A key driver of the cost-effectiveness estimates in this population are the source of efficacy data used in the model. The Bousquet study is more favourable for ICS/LABA as it was the only study that reported the asthma control outcome in which MART had fewer control days, and the Patel study is more favourable for MART, with a much larger difference in exacerbation rate between the two arms. Drug costs also had a large impact on the ICER, given the small incremental costs and QALYs in the base-case. A scenario of interest to the committee was that which excluded symptom status from the analysis given the limitations in the data informing this aspect, and this scenario resulted in MART being the dominant strategy (less costly and more effective).

Table 10: Probabilistic results, escalation to moderate-dose MART in adults

Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER	% cost-effective[(a)]
Moderate-dose MART	£2,144	3.478	-	-	-	40.56%
Moderate/high-dose ICS/LABA + SABA PRN	£2,161	3.482	£16	0.003	£4,769	59.44%

(a) Cost-effective at a threshold of £20,000 per QALY gained

The analysis in children comparing paediatric low-dose MART with paediatric low-dose ICS/LABA + SABA PRN and with paediatric moderate-dose ICS + SABA PRN had consistent results in the deterministic base-case, probabilistic analysis and scenario analyses, with the MART regimen being dominant (less costly and more effective) over both other strategies except in two scenarios. In the two scenarios where MART was not dominant (when the minimum drug costs were used, and when the HSE utility multipliers were used) the ICER was below £20,000 per QALY for MART compared with either ICS/LABA or ICS.

Table 11: Probabilistic results, escalation to paediatric low-dose MART in children

Strategy	Mean cost	Mean QALYs	Incremental cost	Incremental QALYs	ICER	% cost-effective[(a)]
Paediatric low-dose MART	£816	4.329	-	-	-	84.90%
Paediatric moderate-dose ICS + SABA PRN	£838	4.321	£22	-0.008	Dominated	14.46%
Paediatric low-dose ICS/LABA + SABA PRN	£990	4.316	£174	-0.012	Dominated	0.64%

(a) Cost-effective at a threshold of £20,000 per QALY gained

1.1.11 Evidence statements

Economic

- One cost utility analysis in children (6 to 14 years) with asthma requiring frequent SABA relief, found that regular low dose ICS + montelukast dominated low dose ICS/LABA combination (more effective and less costly) and was more cost effective than low dose ICS (ICER: £6,827 per QALY gained). This study was assessed as partially applicable with potentially serious limitations.
- One cost utility analysis in people aged 12 years and older with uncontrolled asthma, previously treated with ICS, found that moderate-dose ICS+LTRA was cost effective compared to moderate-dose ICS+LABA (ICER: £11,919 per QALY gained). This study was assessed as partially applicable with potentially serious limitations.
- One cost utility analysis in adults over 16 years of age, whose asthma has remained uncontrolled using routine low dose ICS and SABA for symptom relief, found that ICS+LTRA was cost effective compared to ICS+LABA (ICER for ICS+LABA vs ICS+LTRA: £56,977 per QALY gained). The study also found that ICS+LTRA dominated moderate ICS and low dose ICS. This analysis was assessed as partially applicable with potentially serious limitations.
- One review in adults and children over 8 years of age with persistent asthma included cost-effectiveness analyses comparing low and moderate dose MART regimes with various doses of ICS/LABA or ICS maintenance treatment and SABA as the as-needed reliever, based on separate RCTs. This analysis was assessed as partially applicable with potentially serious limitations.
  - For trials in the first treatment change, the analysis found that low-dose MART had fewer severe exacerbations than low-dose ICS/LABA + SABA, but that based on one trial (Rabe 2006) low-dose MART costs an additional £82 per exacerbation avoided, and in another trial (O'Byrne 2005) low-dose MART was dominant.
  - For trials in the second treatment change there were comparisons between low-dose MART and both moderate-dose ICS/LABA + SABA (Kuna 2007) and moderate-dose ICS + SABA (O'Byrne 2005), and also between moderate-dose MART and high-dose ICS/LABA + SABA (Bousquet 2007, Vogelmeier 2005). For the analyses based on the trials reported by Kuna and O'Byrne, low-dose MART was dominant over both moderate-dose ICS/LABA + SABA, and moderate-dose ICS + SABA, respectively. For the analyses comparing moderate-dose MART with high-dose ICS/LABA + SABA, it was found that moderate-dose MART cost an additional £868 and £458 per exacerbation when based on Bousquet and Vogelmeier, respectively.
- Two cost utility analysis in adults over 18 years of age, whose asthma has remained uncontrolled using moderate or high dose ICS and LABA, found that LABA/LAMA/ICS dominated (less costly and more effective) ICS/LABA plus LAMA and either dominated or was cost effective compared to ICS/LABA (ICER vs ICS/LABA in Mangia 2021: £12,331 to 14,601 per QALY gained). These analyses were assessed as partially applicable with potentially serious limitations.
- An original cost utility analysis comparing low-dose MART with low/moderate-dose ICS/LABA + SABA PRN in adults, found that low-dose MART would be considered cost-effective at a threshold of £20,000 per QALY, with an ICER of £6,382 compared with low/moderate-dose ICS/LABA. The analysis was assessed as directly applicable with minor limitations.
- An original cost utility analysis comparing moderate-dose MART with moderate/high-dose ICS/LABA + SABA PRN in adults, found that in the base-case moderate-dose MART was less cost-effective than moderate/high-dose ICS/LABA, with the latter having an ICER of £4,769 per QALY gained over moderate-dose MART. A key scenario analysis where symptom status was excluded due to uncertainty in the clinical evidence, resulted in

moderate-dose MART being dominant (less costly and more effective) over moderate/high-dose ICS/LABA + SABA. The analysis was assessed as directly applicable with minor limitations.

- An original cost utility analysis comparing paediatric low-dose MART with paediatric low-dose ICS/LABA + SABA PRN or paediatric moderate-dose ICS + SABA PRN in children, found that paediatric low-dose MART would be dominant (less costly and more effective) over both other strategies. The analysis was assessed as directly applicable with minor limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The purpose of asthma medication is to relieve symptoms, improve quality of life and prevent exacerbations, the need for hospitalisation and asthma deaths. The occurrence of severe asthma exacerbations is of major importance as these are associated with an increased risk of death and have a significant deleterious effect on quality of life. The outcomes considered for this review were severe asthma exacerbations, mortality, quality of life, asthma control, hospital admissions, reliever/rescue medication use, lung function, general adverse events, and specific adverse events; linear growth, pneumonia, adrenal insufficiency, bone mineral density and inflammatory markers. Whilst all outcomes were analysed with equal importance, for the purposes of decision making the committee agreed that asthma exacerbations and mortality were the most important outcomes. In keeping with this consensus, the committee agreed that the threshold for clinical importance for severe asthma exacerbations should be set at 30 events per 1000 people.

Adults and young people aged ≥12 years (3.2a)

Evidence was identified for all comparisons of interest. However, no evidence was identified for the outcome measures of quality of life, adrenal insufficiency, bone mineral density or inflammatory markers.

Adults and young people aged ≥12 years (3.2b)

No evidence was identified for the comparisons: MART versus MART plus LAMA; or MART versus MART plus montelukast (LTRA). No evidence was identified for any comparison for bone mineral density.

Children aged 5-11 years

No evidence was identified for the comparison between MART and regular low-dose ICS with montelukast (plus as needed SABA). Additionally, no evidence was identified for any comparison for asthma control, linear growth, bone mineral density or inflammatory markers.

Children under 5 years

No evidence was identified for intermittent montelukast, regular low/moderate dose ICS/LABA combination or intermittent increases in ICS dose in children under 5 years. Evidence was identified for regular montelukast and indirect interventions, namely regular ICS, as-needed ICS/SABA and as-needed SABA. No evidence was identified for quality of life, asthma control, linear growth, bone mineral density or inflammatory markers.

1.1.12.2 The quality of the evidence

Adults and young people aged ≥12 years (3.2a)

Fifteen RCTs and one post-hoc analysis of three RCTs (16 papers) were identified, twelve of which compared regular low-dose ICS/LABA to regular low-dose ICS, two that compared MART to low-dose ICS with SABA as-needed and three that compared MART to low-dose ICS/LABA with SABA as-needed. Evidence from these papers ranged from moderate to very low quality, with the majority being very low quality. Most of the evidence was downgraded due to risk of bias arising from concerns surrounding the randomisation method and concerns around deviations from the intended interventions, mostly due to a lack of adherence monitoring. Additionally, a large amount of evidence was downgraded due to imprecision, largely due to the rare occurrence of specific adverse events such as mortality, hospital admissions and pneumonia. The committee acknowledged these issues but felt that

they were able to make recommendations as the evidence aligned with their clinical experience.

Indirect evidence was identified for pneumonia, with three studies reporting respiratory tract infections. However, this evidence was very low quality due to imprecision, risk of bias and indirectness. All evidence for the comparison between MART and low-dose ICS/LABA with SABA as-needed was downgraded by one increment due to population indirectness. This was due to the participants in the three included studies being treated with moderate-dose ICS prior to study entry, rather than low-dose as specified in this review protocol.

Adults and young people aged ≥12 years (3.2b)

Fifty-one RCTs were identified in total. Six studies compared the MART regime to regular moderate/high dose ICS/LABA with SABA as needed and two studies compared MART to regular moderate/high dose ICS with SABA as needed. A single study (Wang et al, 2015) comprised three trial arms consistent with the protocol so contributed to evidence for three comparisons: it was the only study comparing regular moderate/high dose ICS/LABA versus regular low/moderate dose ICS/LABA plus montelukast; one of 4 studies comparing regular moderate/high dose ICS/LABA versus regular low/moderate dose ICS/LABA plus LAMA; and one of two studies comparing regular low/moderate dose ICS/LABA plus montelukast versus regular low/moderate dose ICS/LABA plus LAMA.

Most of the evidence identified (30 studies) compared regular moderate/high dose ICS/LABA with regular moderate/high dose ICS. Two studies compared regular moderate/high dose ICS/LABA with regular low/moderate dose ICS plus montelukast and three studies compared regular moderate/high dose ICS/LABA with regular low/moderate dose ICS plus LAMA. Finally, three studies compared regular moderate/high dose ICS with regular low/moderate dose ICS plus montelukast. For all these comparisons, SABA was available as needed in each arm.

Overall, evidence from the studies ranged from high to very low quality. For most comparisons the certainty of findings for each outcome varied from very low to moderate. However, findings for some outcomes for the comparison of MART versus regular moderate/high ICS/LABA (with SABA as needed) were high certainty. Evidence for three comparisons were all low or very low certainty: regular moderate/high dose ICS/LABA versus regular low/moderate dose ICS/LABA plus montelukast; regular low/moderate dose ICS/LABA plus montelukast versus regular low/moderate dose ICS/LABA plus LAMA; and regular moderate/high dose ICS/LABA versus regular low/moderate dose ICS plus montelukast.

The majority of the evidence identified was in studies funded by the pharmaceutical industry; where ≥10 studies were available for any particular outcome for any comparison, publication bias was assessed by funnel plots and reflected in the certainty of evidence in GRADE. Most of the evidence was downgraded due to concerns about the risk of bias. Reasons included: unclear randomisation or analysis method, deviations from the intended interventions or exclusion criteria, lack of adherence monitoring, inclusion of an open-label study, missing outcome data or high dropout rate and reasons for discontinuation related to participant's health status. A large amount of evidence was downgraded due to imprecision; this is due to the rare occurrence of specific adverse events such as mortality, hospital admissions and pneumonia or adrenal insufficiency, or in some cases the small sample size of participants. A large amount of evidence compared regular moderate/high dose ICS/LABA with regular moderate/high dose ICS and for this comparison the evidence for some outcomes was downgraded due to unexplained heterogeneity. In some instances, findings were downgraded due to indirectness of population or the intervention, due to medications taken prior to entry of the study, or changes (including to doses) to medications taking during the intervention, respectively. Other issues affecting population indirectness include age of participants and proportion with uncontrolled asthma.

Children aged 5-11 years

Eight RCTs were identified in children all of which compared regular paediatric moderate/high dose ICS to regular paediatric moderate/high dose ICS/LABA. Two RCTs had an additional trial arm (3 trial arms) that also investigated effectiveness of either MART or regular paediatric moderate/high dose ICS with montelukast (plus as needed SABA). Therefore, one RCT compared regular paediatric moderate/high dose ICS plus as needed SABA to MART, and regular paediatric moderate dose ICS/LABA plus as needed SABA to MART. Similarly, one RCT compared regular paediatric moderate/high dose ICS to regular paediatric moderate dose ICS with montelukast, and regular paediatric moderate dose ICS/LABA to regular paediatric low dose ICS with montelukast. Evidence from these papers ranged from moderate to very low quality, with the majority being very low quality. All evidence involving comparisons with low regular ICS with montelukast was very low quality.

Evidence was commonly downgraded due to risk of bias in studies due to lack of information about randomisation or adherence to interventions, missing data, and lack of pre-specification of analyses in protocols; in one case downgrading was also due to the open-label nature of the RCT.

Additionally, a large amount of evidence was downgraded due to imprecision; this was sometimes due to the rare occurrence of specific adverse events such as mortality, adrenal insufficiency and pneumonia, but also because confidence intervals reflect very small sample sizes in some studies. Some evidence was also downgraded for population indirectness due to containing a mixture of children and adolescents. One finding was downgraded due to high heterogeneity in the evidence that could not be explained with pre-specified subgroup analyses.

Children under 5 years

Two RCTs, one of which was a crossover study, were identified in infants aged between 1-5 years of age. Comparisons made were between regular ICS and as needed ICS/SABA, regular ICS and regular montelukast, and as needed ICS/SABA vs regular montelukast.

1.1.12.3 Benefits and harms

Adults and young people aged ≥12 years (3.2a)

Regular low-dose ICS/LABA vs regular low-dose ICS

For the comparison between regular low-dose ICS/LABA and regular low-dose ICS, very low quality evidence from two RCTs showed that there were less severe asthma exacerbations at ≥6 months, with 20 fewer events per 1,000 participants (80 fewer to 20 more) in the ICS/LABA arm; this difference failed to meet the pre-set definition for clinical importance. However, was a clinically important benefit of ICS/LABA on severe exacerbation rate, with a rate ratio of 0.77 (95%CI 0.57-1.05) indicating a 23% reduction in severe exacerbation rate with ICS/LABA, albeit from very low quality evidence from three RCTs. Very low quality evidence showed a clinically important benefit of low-dose ICS/LABA on PEF values, with a mean difference of 22.5 L/min (95%CI 18.91 higher to 26.08 higher) higher than low-dose ICS.

MART vs regular low-dose ICS with SABA as needed

For the comparison between MART and regular low-dose ICS with SABA as-needed, low quality evidence from a single RCT showed a clinically important benefit of MART on severe asthma exacerbations at ≥6 months, with 56 fewer events per 1,000 participants (95%CI 76 fewer to 29 fewer; RR 0.52, 95%CI 0.35-0.75). This was supported by the severe exacerbation rate data, with a moderate quality evidence from a single study reporting a rate

ratio of 0.24 (95%CI 0.20-0.27), indicating a 76% reduction in severe exacerbation rate with MART. A clinically important benefit of MART was seen on lung function (PEF), with moderate quality evidence from a single RCT reporting a mean difference of 25 L/min (95%CI 19.4 higher to 30.6 higher) in favour of MART. No other clinically important differences were identified.

MART vs regular low-dose ICS/LABA with SABA as needed

For the comparison of MART versus regular low dose ICS/LABA with SABA as needed, moderate quality evidence from two RCTs showed a clinically important benefit of MART on severe asthma exacerbations at ≥6 months with 72 fewer events per 1,000 participants (89 fewer to 52 fewer; RR 0.67, 95%CI 0.59-0.76). No clinically important differences between treatment arms, were identified for any other outcome.

Children aged 5-11 years

Regular paediatric moderate/high dose ICS/LABA vs regular paediatric moderate/high dose ICS

For the comparison between regular paediatric moderate dose ICS/LABA and regular paediatric moderate/high dose ICS, clinically important differences were identified for severe asthma exacerbations at ≥6 months and hospital admissions, but the treatment arm producing the better outcome was not consistent and for both outcomes the certainty of evidence was very low. For severe asthma exacerbations at ≥6 months, the risk difference was 95 more per 1000 (16 more to 215 more), indicating a clinically important benefit of paediatric moderate/high dose ICS. For hospital admissions, the risk difference was 53 fewer per 1000 (81 fewer to 30 more) for regular paediatric moderate dose ICS/LABA, therefore showing a clinically important benefit in the opposite direction. In addition, the committee noted that severe exacerbations in the 3-5 month period were lower with ICS/LABA, although the difference was modest. They were not able to account for these inconsistent results.

No clinically important difference favouring either arm was identified for any other outcome.

MART vs regular paediatric moderate/high dose ICS/LABA with SABA as needed

For the comparison between MART and regular paediatric moderate/high dose ICS/LABA with SABA as needed, clinically important differences were identified for severe asthma exacerbations, severe exacerbation rates and adverse events. There were 222 fewer severe asthma exacerbations per 1,000 participants (265 fewer to 145 fewer) with MART. The same direction of effect was seen in severe exacerbation rates, with a rate ratio of 4.77 (2.49 to 9.14) indicating a 377% increase in events with paediatric moderate/high ICS/LABA with SABA as needed. Similarly, there were fewer adverse events with MART, with a difference of 120 per 1,000 (133 fewer to 64 fewer). All data was of moderate quality, although it was acknowledged that this was from a single RCT that contained a relatively small number of participants. No clinically important difference favouring either arm was identified for any other outcome.

MART vs regular paediatric moderate/high dose ICS with SABA as needed

For the comparison between MART and regular paediatric moderate/high dose ICS with SABA as needed, clinically important differences were identified for severe asthma exacerbations and severe exacerbation rate. There were 113 fewer (157 fewer to 26 fewer) severe exacerbations per 1,000 participants with MART, with severe exacerbation rate showing a similar benefit with a risk ratio of 3.24 (1.63 to 6.42) reflecting a 224% increase in events with paediatric moderate/high dose ICS with SABA as needed. This evidence was low

to moderate quality and came from a single RCT with a limited number of participants. No clinically important difference favouring either arm was identified for any other outcome.

Regular paediatric moderate/high dose ICS vs regular paediatric moderate dose ICS plus montelukast

For the comparison of regular paediatric moderate/high dose ICS versus paediatric moderate dose ICS plus montelukast, the only clinically important difference identified was for quality of life. A mean difference of 0.55 (1.56 lower to 0.46 higher) was identified in favour of ICS plus montelukast, albeit from very low quality evidence that was downgraded as a result of population indirectness, very serious risk of bias and very serious imprecision. Furthermore, this evidence was from a single small study, limiting the confidence of the committee to make recommendations based on the finding. No clinically important difference favouring either arm was identified for any other outcome, including severe asthma exacerbations at ≥6 months, with very low quality evidence showing a difference of 8 events per 1,000 people (77 fewer to 1201 more) in favour of ICS plus montelukast.

Regular paediatric moderate/high dose ICS/LABA vs regular paediatric moderate dose ICS plus montelukast

For the comparison between regular paediatric moderate dose ICS/LABA versus regular paediatric moderate dose ICS plus montelukast, clinically important differences were seen in severe asthma exacerbations, quality of life and lung function (FEV_1). There were 250 fewer (38 fewer to 2,400 more) severe exacerbations per 1,000 participants with ICS/LABA compared to ICS with montelukast. Lung function showed the same direction of effect, with a 10.99% greater increase in FEV_1 (3.92 lower to 25.9 higher) with ICS/LABA compared to ICS with montelukast. In contrast, quality of life assessed with the Paediatric Asthma Quality of Life Questionnaire showed a 0.74 lower (2.07 lower to 0.59 higher) change over with ICS/LABA compared to ICS plus montelukast. All data for this comparison was very low quality, coming from the same study as the previous comparison (paediatric moderate/high dose ICS vs regular paediatric moderate dose ICS plus montelukast) with the same limitations. No clinically important difference favouring either arm was identified for any other outcome.

Children under 5 years

Regular ICS vs as-needed ICS/SABA

For the comparison between regular ICS and as-needed ICS/SABA, very low quality evidence from a single RCT reported a clinically important benefit of regular ICS, with 88 fewer severe asthma exacerbations per 1,000 participants (95%CI 141 to 14 fewer) compared to as-needed ICS/SABA (RR 0.68; 95%CI 0.49-0.95). No other outcomes showed a clinically important benefit of either intervention.

Regular ICS vs regular montelukast

For the comparison between regular ICS and regular montelukast there was a clinically important benefit of regular ICS on severe asthma exacerbations at both the 3-5 and ≥6-month time points. Low quality evidence from a single study showed 150 fewer exacerbations per 1,000 participants (95%CI 201 to 82 fewer; RR 0.56, 95%CI 0.41-0.76) with regular ICS compared to regular montelukast after 16 weeks. Following the same pattern, very low quality evidence from a different RCT showed 152 fewer exacerbations per 1,000 participants (95%CI 230 to 30 fewer; RR 0.59, 95%CI 0.38-0.92) with regular ICS compared to regular montelukast. No other outcomes showed a clinically important benefit of either intervention.

As-needed ICS/SABA vs regular montelukast

For the comparison between as-needed ICS and regular montelukast, very low quality evidence from a single RCT reported a clinically important benefit of as needed ICS/SABA with 65 fewer severe asthma exacerbations per 1,000 participants (95%CI 129 fewer to 20 more; RR 0.81, 95%CI 0.62-1.06) compared to regular montelukast. No other outcomes showed a clinically important benefit of either intervention.

3.2b Further step-up treatment adults and young people aged ≥12 years with uncontrolled asthma

MART vs regular moderate/high dose ICS/LABA with SABA as needed

For the comparison between MART and moderate/high dose ICS/LABA with SABA as needed, there was a clinically important benefit of MART on severe asthma exacerbations at ≥6 months, with 35 fewer events per 1000 participants (95%CI 47 fewer to 21 more; Peto OR 0.72, 95%CI 0.63-0.83) identified from 5 RCTs with moderate certainty of the evidence. This benefit was reflected in the severe exacerbation rate data, showing a rate ratio of 0.70 (95%CI 0.61-0.81) from 4 RCTs, indicating a 30% reduction in exacerbation rate with MART. No other clinically important benefits were identified for either intervention.

MART vs regular moderate/high dose ICS with SABA as needed

For the comparison between ICS/formoterol MART and moderate/high dose ICS with SABA as needed, there was a clinically important benefit of MART on severe asthma exacerbations at ≥6 months, with 88 fewer events per 1000 participants (95%CI 107 fewer to 68 fewer; RR 0.62, 95%CI 0.54-0.71) identified from 2 RCTs with moderate certainty of the evidence. This benefit was reflected in the severe exacerbation rate data, showing a risk ratio of 0.57 (95%CI 0.48-0.68) from one RCT, also with moderate certainty, indicating a 43% reduction in exacerbation rate with MART. A clinically important benefit of MART was also seen in lung function (peak expiratory flow), with a mean difference of 18.86 L/min (95%CI 15.76-21.96) identified from 2 RCTs with low certainty of the evidence. No other clinically important benefits were identified for either intervention.

Regular moderate/high dose ICS/LABA vs regular low/moderate dose ICS/LABA plus montelukast

No severe asthma exacerbation data was identified for this comparison. No clinically important benefits were identified for any outcomes.

Regular low/moderate dose ICS/LABA plus LAMA vs regular moderate/high dose ICS/LABA

For the comparison between regular moderate/high dose ICS/LABA and regular low/moderate dose ICS/LABA plus LAMA, very low quality evidence from two RCTs did not show a clinically important difference in severe asthma exacerbations at ≥6 months, with 20 fewer events per 1000 participants (RR 0.89, 95%CI 0.77-1.02) in the ICS/LABA arm. A clinically important benefit of ICS/LABA was seen on mortality, with data from three RCTs showing 1 fewer event per 1000 participants (Peto OR 0.63, 95%CI 0.21-1.87), although there was very low certainty of the estimate. A clinically important benefit of ICS/LABA plus LAMA was seen on inflammatory markers, with data from a single RCT showing a 15.63 (95%CI 10.89-20.37) ppb increase in FeNO with ICS/LABA, although the certainty of the evidence was very low. No further clinically important differences were found.

Regular moderate/high dose ICS/LABA vs regular moderate/high dose ICS

For the comparison between moderate/high dose ICS/LABA and moderate/high dose ICS there was a clinically important benefit of ICS/LABA on severe asthma exacerbations at ≥6 months, with 47 fewer events per 1000 participants (95%CI 62 fewer to 30 fewer; Peto OR 0.70, 95%CI 0.61-0.80) identified from 10 RCTs with low certainty of the evidence. This benefit was also seen in the severe exacerbation rate data with a rate ratio of 0.74 (95%CI

0.65-0.84) being shown from five RCTs with a low certainty of the evidence, indicating a 26% reduction in severe exacerbation rate with ICS/LABA. A clinically important benefit of ICS/LABA was also seen in lung function (PEF) with a mean difference of 24.31 (95%CI 19.83 higher to 28.78 higher) L/min compared to ICS, identified from 16 RCTs with very low certainty of the evidence. A clinically important benefit of ICS/LABA was also seen in adrenal insufficiency, expressed as the 0-24h AUC of serum cortisol, with a mean difference of 0.2 (95%CI 0.02 higher to 0.38 higher) identified from a single study with very low certainty of the evidence.

Regular moderate/high dose ICS/LABA vs regular low/moderate dose ICS plus montelukast

For the comparison between moderate/high dose ICS/LABA and low/moderate dose ICS with montelukast there was no clinically important difference in severe asthma exacerbations at 3-5 months, with 6 more events per 1,000 participants (95%CI 17 fewer to 46 more; RR 1.12, 95%CI 0.65-1.94) with ICS/LABA. There was no data covering a longer time period. A clinically important benefit of ICS/LABA was seen for lung function (PEF), with a mean difference of 24.2 (95%CI 5.6 lower to 54 higher) L/min identified from one RCT with very low certainty of the evidence. No further clinically important differences were identified.

Regular low/moderate dose ICS/LABA plus LAMA vs regular low/moderate dose ICS/LABA plus montelukast

For the comparison between ICS/LABA plus LAMA and ICS/LABA plus montelukast there was a clinically important benefit of ICS/LABA plus LAMA on severe asthma exacerbations at ≥6 months, with very low quality evidence from a single RCT reporting 41 more events per 1,000 participants (95%CI 98 fewer to 450 more; RR 1.24, 95%CI 0.43-3.61) in the ICS/LABA plus montelukast arm. Additionally, a clinically important benefit of ICS/LABA plus LAMA was seen on lung function (FEV_1), with a difference of -3 (95%CI 4.85 lower to 1.15 lower) percent of predicted with ICS/LABA plus montelukast identified from a single RCT with low certainty of the evidence. No further clinically important differences were identified.

Regular moderate/high dose ICS/LABA vs regular low/moderate dose ICS plus LAMA

For the comparison between ICS/LABA and ICS plus LAMA there was no clinically important difference in severe asthma exacerbations at ≥6 months, with very low quality data from one RCT reporting 12 more events per 1,000 participants (95%CI 10 fewer to 45 more; RR 1.23, 95%CI 0.81-1.87) with ICS/LABA. There were no clinically important differences for any outcomes.

Regular moderate/high dose ICS vs regular low/moderate dose ICS plus montelukast

For the comparison between ICS and ICS plus montelukast there was no clinically important difference in severe asthma exacerbations at 3-5 months, with low quality data from two RCTs reporting 16 more events per 1,000 participants (95%CI 5 fewer to 55 more; RR 1.58, 95%CI 0.83-3.02) in the ICS arm. A clinically important benefit of ICS plus montelukast was seen in severe exacerbation rate, with a rate ratio of 0.45 (95%CI 0.20-0.99) indicating a 55% reduction in severe exacerbation rate with ICS plus montelukast, albeit from a single RCT with low certainty of the evidence. No further clinically important differences were identified.

1.1.12.4 Cost effectiveness and resource use

People aged over 12 years

For the initial escalation of treatment, one cost effectiveness study (Wickstrom 2009) was identified in adults which found low-dose MART and moderate-dose MART compared with low/moderate and moderate/high-dose ICS/LABA plus SABA were either less costly and resulted in fewer severe exacerbations or more costly and resulted in fewer severe

exacerbation. This cost effectiveness analysis was assessed as partially applicable with potentially serious limitations. The committee considered the Wickstrom et al (2009) study when discussing the cost-effectiveness of stepping up therapy in people who have uncontrolled asthma, but felt that more robust evidence was required to determine whether MART would be cost-effective compared with ICS/LABA plus SABA in adults at low and moderate dose (and in children, see section below) and so this area was prioritised for economic modelling.

The new economic analysis included three separate analyses, two in adults and one in children. The analyses in adults were: low-dose MART versus low/moderate-dose ICS/LABA + SABA PRN in adults and moderate-dose MART versus moderate/high-dose ICS/LABA + SABA PRN in adults.

The committee recommended that low-dose MART should be used for the initial escalation of treatment for adults with uncontrolled asthma; the results of the economic analysis demonstrated that this was a cost-effective use of NHS resources compared with the alternative of using ICS/LABA plus SABA, with MART having an ICER below £20,000 per QALY gained in the base-case and all scenario analyses. Additionally, the committee noted that a simpler approach is important to patients, so the convenience of having a single inhaler for maintenance and reliever therapy is beneficial.

For the second escalation of treatment for adults whose asthma is uncontrolled on either low-dose MART or moderate-dose ICS/LABA plus SABA or ICS plus SABA, the results of the economic analysis were less clear. The committee considered the model base-case and scenario analyses, as well as the strength of the clinical data informing those analyses when making their recommendations. Although the model base-case indicated that moderate-dose MART was less cost-effective than moderate/high dose ICS/LABA plus SABA, the committee also considered a scenario analysis to be equally plausible, where symptom status was removed from the model on the basis of the clinical evidence for this population being less robust, and the result of this scenario favoured the moderate-dose MART regimen. The committee also took into account the simplicity for patients of remaining on a MART regimen, given the previous recommended step in the treatment pathway was low-dose MART. They felt that changing back to separate inhalers may not make sense in practice. Therefore, a recommendation to offer moderate-dose MART was made for adults uncontrolled on low-dose MART.

The committee noted that for those who remain uncontrolled at this stage despite good adherence, the evidence on what to do next is not clear from the available evidence. They noted that in this population checking the FeNO level (if available) and the blood eosinophil count should be considered and if either of these is raised then a referral to a specialist in asthma care should be made. This is because a person who is uncontrolled on moderate dose MART, and therefore using their ICS/formoterol reliever inhaler regularly, is effectively on high dose ICS and if this is failing to control their airway inflammation they are at increased risk of severe asthma attacks. If neither FeNO or eosinophil count was raised, based on the clinical evidence looking at the addition of montelukast or LAMA to moderate dose ICS or moderate-dose ICS/LABA, the committee considered that the next step would be the addition of either montelukast or LAMA. No health economic evidence was identified for the addition of either montelukast or LAMA to MART. Clinical evidence was available looking at the addition of either montelukast or a LAMA to baseline treatment with moderate-dose ICS or moderate dose ICS/LABA, but the 2 options were only compared directly in 2 small studies. Although the comparison showed a reduction in exacerbations with a LAMA added to ICS/LABA compared with adding montelukast to ICS/LABA, the committee did not have much confidence in the result because of the small study population. Although not direct evidence for an adult population stepping up from MART, two health economic analyses were identified (Price 2011 and NICE 2017) which found that moderate dose ICS plus montelukast was cost effective compared to moderate dose ICS/LABA or moderate ICS or low dose ICS. Both studies were assessed as partially applicable with minor limitations.

Although no health economic evidence was identified for LAMA as an addition to MART, two cost utility studies were identified exploring the addition of LAMA in patients uncontrolled with high dose ICS/LABA (Mangia 2021 and Mtibaa 2021). Both studies compared the triple inhaler (ICS/LABA/LAMA) versus ICS/LABA versus ICS/LABA plus LAMA. The studies found that a triple inhaler was more cost effective than adding LAMA to ICS/LABA. These studies however were not done in the context of MART, and people were using SABA for relief. There was no specific economic or clinical evidence to suggest the benefit of the triple inhaler in the context of stepping up from MART.

When the committee discussed whether an LTRA or LAMA should be used as the next step up they noted that it would be simpler to add an LTRA than a LAMA because the latter would involve teaching the person with asthma how to use an additional inhaler device, and the requirement for 2 inhalers is also less environmentally desirable. An LTRA is also cheaper, but there is a risk of significant side effects, particularly neuropsychiatric disturbances. These neuropsychiatric disturbances were not incorporated in the health economic analyses of montelukast identified in the literature due to poor reporting of these adverse events at the time of their publication. The committee noted that for the more common adverse events such as sleep disturbances, and agitation would not require costly healthcare interventions to manage these. The more severe adverse events such as hallucinations and suicidal thinking would require more costly intervention, such as psychiatric referrals and hospitalisation, but these side effects are very rare and therefore their management unlikely to have a significant resource impact to the NHS. It was agreed therefore that there was no convincing reason to recommend one option over the other and that the choice of the person with asthma should decide which should be tried first after a discussion of the potential benefits and harms which should include the risk of neuropsychiatric side effects with montelukast

When considering the treatment pathway they were recommending to in the guideline, the committee agreed to not specify using the triple inhaler as they did not want people to go have to back to SABA for relief and considered the cost of having a triple inhaler for maintenance and a combination inhaler for relief would be more costly than having combination inhaler plus a LAMA inhaler.

Children aged 5 to 11 years

In the absence of published evidence in children for the use of MART. A new economic analysis was conducted in children comparing paediatric low-dose MART versus paediatric low-dose ICS/LABA plus SABA PRN versus paediatric moderate-dose ICS plus SABA PRN. The analysis found that paediatric low-dose MART is likely to be dominant (less costly and more effective) over either paediatric low-dose ICS/LABA plus SABA or paediatric moderate-dose ICS plus SABA, and therefore the committee recommended that paediatric low-dose MART be considered for stepping up treatment in this population if the child is able to manage the MART regimen and the healthcare professional is willing to prescribe it.

The committee made a consider recommendations to increase to paediatric moderate-dose MART in children uncontrolled on paediatric low-dose MART. This weaker ‘consider’ recommendation was made to reflect the clinical uncertainty and absence of health economic evidence for this.

The committee noted that some children may struggle to use a MART regimen, as they may not find the available inhalers suitable, and that healthcare professionals may not be willing to prescribe MART when it is unlicensed in this age group. Therefore, they considered alternative choices to MART for those uncontrolled on paediatric low-dose ICS. These options included adding LTRA or LABA, or increasing maintenance ICS. The clinical evidence did not show one option was superior to any other and so to limit ICS exposure and due to the lower cost compared to ICS/LABA, they considered adding montelukast to

paediatric low-dose ICS plus SABA PRN as the first step up. This is supported by a cost-utility analysis in children (aged 6-14 years) by Lenney 2013, which found that in children with uncontrolled asthma, regular low dose ICS/LABA plus regular montelukast was more cost effective than regular low dose ICS or regular low-dose ICS/LABA combination. This study was assessed as partially applicable with potentially serious limitations. The committee noted again the potential for neuropsychiatric side effects with montelukast, and that this should only be started after a discussion of the potential benefits and harms.

If further step up is required due to uncontrolled asthma, the committee recommended twice daily paediatric low-dose ICS/LABA inhaler (with or without montelukast depending on side effects and whether it had produced any benefit at all when added). The ICS could then be further increased to paediatric moderate dose if control remained inadequate. These recommendations are in line with current practice.

Children under 5

No health economic evidence was identified for this population. The recommendations made reflect current practice.

For both adults and children these recommendations will be a change in practice for newly diagnosed asthma. People with an existing diagnosis of asthma who are stable on their current therapy do not have to switch treatment. Adults on current pathways who need an increase in treatment will be switched to MART, but this is one of the current options. There should therefore not be significant disruption to asthma care. The new treatment steps are cost-effective for the NHS and will reduce the number of exacerbations requiring treatment and the number of hospital admissions for asthma.

1.1.12.5 Other factors the committee took into account

A major issue addressed by the committee was the lack of evidence for stepping up treatment from as-needed ICS/formoterol, which has been recommended as the first-line treatment option for newly diagnosed asthma in adults. This is a new therapeutic approach and is rarely used at present in the UK, hence research studies have not been carried out in a population in whom this is the baseline treatment. All evidence identified was in people stepping up treatment from as-needed SABA or regular low-dose ICS, which has been the accepted first-line treatment in the UK. The evidence identified presents a strong argument for switching patients with asthma who are uncontrolled on these therapies to MART, but it is less clear if stepping up from as-needed ICS/formoterol to MART will provide the same therapeutic effect. This is not a problem in children since the committee recommended traditional treatment with a regular ICS inhaler plus PRN SABA as first line treatment. It was agreed that this was an important area for further research that should be conducted in the future as more people begin receiving as-needed ICS/formoterol.

One key area of concern arising from the discussion of MART was over-exposure to ICS. The majority of people with asthma are currently treated with salbutamol as their as-needed medication. The effects of salbutamol are rapid and fade relatively quickly with little to no lasting effects providing salbutamol is not used to excess. Using ICS/formoterol as a maintenance and reliever medication provides simplicity for the user, but potentially comes with a risk of over-exposure to ICS which, over a prolonged period of time could produce a variety of health risks, including adrenal insufficiency and reduced growth rates in children. This is particularly important because MART is not currently licensed in children in the UK. The committee were reassured by the adverse event data in the evidence they considered which did not show unfavourable outcomes with MART, and also by their personal experience which suggests that overuse of ICS/formoterol in the MART regimen is rare. The Committee agreed that it was important to consider the individual patient's history and relationship with their reliever medication before switching to MART, and that education would be needed to ensure safe use. They also noted that the MART regimen places upper limits on the number of as-needed inhalations of ICS/formoterol which can be used per day.

Another consideration was the impact of inhaler choice on environmental factors. The significant carbon emissions of metered dose inhalers (MDIs) was discussed at length, with the committee agreeing that dry powder inhalers (DPIs) are preferable due to their lower carbon footprint. Whilst this is an important consideration, the committee agreed that the most important factor in inhaler choice should be the ability of the patient to use the inhaler to support adequate asthma control. The majority of people are able to use DPIs interchangeably with MDIs. However, there is a legitimate concern that in the event of a severe exacerbation some people may be unable to generate suitable inspiratory airflow to obtain relief via a DPI, and this may be a greater risk in children. Overall, clinicians on the committee agreed that there are very few cases where adults may be experiencing a severe enough exacerbation that a DPI is not useable. Nonetheless this may necessitate some people having an MDI containing a SABA to be used with a spacer during exacerbations, and this negates the simplicity of MART for those people. It was also noted that personalised action plans for use of MART during asthma exacerbations require careful consideration and clinician-patient collaboration.

The committee agreed on the general principle that the fewer inhalers people use, the better. This is to support simplicity for users and to encourage adherence to maintenance therapy. The committee strongly reiterated the need for clinician-patient collaboration in order to select the correct inhaler for the participant, and agreed that the NICE asthma decision aid provided a valuable resource for clinicians and patients (https://www.nice.org.uk/guidance/ng80/resources/inhalers-for-asthma-patient-decision-aid-pdf-6727144573T).

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.3, 1.7.4, 1.7.5, 1.7.6, , 1.8.2, 1.8.3, 1.8.4, 1.8.5, 1.8.6, 1.8.7, 1.9.5 and 1.9.6. and the research recommendation on add-on strategies for adults who need additional treatment after initial treatment with ICS/formoterol used PRN (as required). Other evidence supporting recommendations 1.9.5 and 1.9.6 can be found in the evidence review Drug Classes for Initial Management (P).

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for pharmacological management of asthma (drug combination and sequencing)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Drug combinations and sequencing for asthma management.
2.	Review question	What is the most clinically and cost-effective sequence in which to introduce additional drugs or combination of drugs for the management of asthma when initial management fails to provide adequate control?
3.	Objective	To determine which is the best sequence in which to introduce drugs to existing treatment plans when the initial drug treatments fails in the management of asthma.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Asthma
6.	Population	Inclusion: People with a diagnosis of asthma that is not controlled by initial treatment Separate review questions for: 1. Adults and young people (≥12 years) Stratified based on initial treatment: ICS/Formoterol (as needed) vs regular low-dose ICS vs SABA (as needed) 2. Children 5-11 years 3. Children under 5 years Exclusion: • People diagnosed with asthma who are treatment naïve • People who have received additional drugs other than ICS or ICS/LABA • People with severe asthma
7.	Intervention	**Maintenance therapies**

		Step 3.2A : People ≥12 years **All treatment options for this population should be grouped depending upon the as-needed (prn) medication** **3) ICS/LABA** **4) SABA** • Regular low dose ICS (as defined in the NICE table) (budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, flunisolide, triamcinolone) **/** LABA (formoterol, salmeterol, vilanterol or indacaterol) combination inhaler or concurrent inhalers • Regular low dose ICS inhaler 3.2B: People ≥12 years **All treatment options for this population should be grouped depending upon the as-needed (prn) medication** **5) ICS/LABA** **6) SABA** • Regular moderate/high doses ICS/LABA (formoterol, salmeterol or vilanterol) combination inhaler or concurrent inhalers • Regular low/moderate dose ICS/LABA combination inhaler plus montelukast • Regular low/moderate dose ICS/LABA combination inhaler plus LAMA • Regular moderate/high dose ICS inhaler • Regular low/moderate dose ICS inhaler plus montelukast • Regular low/moderate dose ICS inhaler plus LAMA • ICS/SABA combination inhaler prn Children 5-11 years • Regular paediatric moderate/high dose ICS/LABA with SABA prn • Regular paediatric moderate ICS and montelukast with SABA prn • Regular paediatric moderate/high dose ICS with SABA prn

		• Regular paediatric moderate dose ICS/formoterol with ICS/formoterol prn (i.e. MART regime) <u>Children under 5 years (initial treatment: daily ICS)</u> <u>Step2</u> • Moderate dose regular ICS • Intermittent montelukast • Regular montelukast • Regular moderate/high dose ICS/LABA combination • Intermittent increases in ICS dose
8.	Comparator	• Compared to each other
9.	Types of study to be included	• RCT • Systematic reviews of RCTs Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. Minimum study duration: 12 weeks
11.	Context	
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical:

		• Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at 3-5 months and ≥6 months) • Severe exacerbation rate (event rate per person year/rate per patient year) • Mortality (dichotomous outcome at ≥6 months) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months) • Asthma control assessed by a validated questionnaire (ACQ/p ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) • Hospital admissions (dichotomous outcome at ≥3 months and ≥6 months) • Reliever/rescue medication use (continuous outcome at ≥3 months) • Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). *Note: Extract FEV1 %pred over litres if both are reported. If only litres is reported, extract and analyse separately (do not extract both). For children, only use FEV1 %pred.* • Adverse events (to be extracted as general adverse events minus specific adverse events reported below): o Linear growth (continuous outcome at ≥1 year), o Pneumonia frequency (dichotomous outcome at ≥3 months, including lower respiratory and general, in that order, respiratory tract infections, but not including upper respiratory tract infections) o Adrenal insufficiency (as defined by study, including short synacthen test and morning cortisol, dichotomous outcome at ≥3 months) o Bone mineral density (continuous outcome at ≥6 months) • Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.

		10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)

15.	Strategy for data synthesis	Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. Where heterogeneity is present within meta-analysed outcomes, studies of very high/high risk of bias rating will be removed from the analysis to as a first step to resolving heterogeneity. If this does not resolve heterogeneity, then sub-group analysis will be applied.
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Asthma history • Previous exacerbation • No previous exacerbation

		>5 years only: • Atopic comorbidities (e.g. allergic rhinitis, hay fever)		
17.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date			
21.	Anticipated completion date	31 July 2024		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐

		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail chronicasthmamanagement@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
24.	Review team members	 From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Qudsia Malik (Senior systematic reviewer) Clare Jones (Senior systematic reviewer) Toby Sands (Systematic reviewer) Alfredo Mariani (Senior health economist) Lina Gulhane (Head of information specialists) Stephen Deed (Information specialist) Amy Crisp (Senior project manager)		

		Lisa Miles (Technical Analyst)
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10186
28.	Other registration details	N/A
29.	Reference/URL for published protocol	N/A
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
31.	Keywords	N/A

32.	Details of existing review of same topic by same authors	N/A	
33.	Current review status	x	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	N/A	
35.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Table 12: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.

Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).(National Institute for Health and Care Excellence)

Inclusion and exclusion criteria

- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).

	• Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 13: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 28 Dec 2023	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 28 Dec 2023	Randomised controlled trials Systematic review studies Exclusions (conference abstracts, animal studies, letters, comments, editorials, case studies/reports) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2023 Issue 12 of 12 CENTRAL to 2023 Issue 12 of 12	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 28 Dec 2023	Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/

9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	Triamcinolone/ or Budesonide/ or Beclomethasone/ or Fluticasone/ or Mometasone Furoate/
25.	(budesonide or beclomethasone or beclometasone or ciclesonide or fluticasone or flunisolide or triamcinolone or mometasone).ti,ab,kf.
26.	((glucocorticosteroid* or glucocorticoid* or corticosteroid* or cocorticoid* or corticoid* or steroid* or preventer) adj2 inhale*).ti,ab,kf.
27.	ICS.ti,ab.
28.	(Asmabec or Clenil Modulite or Qvar or Alvesco or Pulmicort or Flixotide or Novolizer or Asmanex or Aerobid or Flovent or Becotide).ti,ab,kf.
29.	Albuterol, Ipratropium Drug Combination/ or Budesonide, Formoterol Fumarate Drug Combination/ or Fluticasone-Salmeterol Drug Combination/ or Mometasone Furoate, Formoterol Fumarate Drug Combination/
30.	((combination or MART) adj2 inhaler*).ti,ab,kf.
31.	(("maintenance and reliever" or MART or SMART) adj2 (therap* or treatment*)).ti,ab,kf.
32.	(Fostair or Seretide or DuoResp or Symbicort or Relvar or Fobumix or Ventide or Aerocort).ti,ab,kf.
33.	Leukotriene Antagonists/
34.	(leukotriene receptor antagonist* or leukotriene antagonist* or antileukotriene* or anti leukotriene* or leukotriene modifier* or leukotriene inhibitor* or LTRA or LTRAs).ti,ab,kf.
35.	(zafirlukast or montelukast or pranlukast).ti,ab,kf.
36.	(Accolate or Singulair).ti,ab,kf.
37.	or/24-36
38.	23 and 37
39.	randomized controlled trial.pt.
40.	controlled clinical trial.pt.
41.	randomi#ed.ab.
42.	placebo.ab.
43.	randomly.ab.
44.	clinical trials as topic.sh.
45.	trial.ti.

46.	or/39-45
47.	Meta-Analysis/
48.	Meta-Analysis as Topic/
49.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
50.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
51.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
52.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
53.	(search* adj4 literature).ab.
54.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
55.	cochrane.jw.
56.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
57.	or/47-56
58.	38 and (46 or 57)

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	*budesonide/ or *beclometasone/ or *ciclesonide/ or *fluticasone/ or *flunisolide/ or *triamcinolone/ or *mometasone furoate/
24.	(budesonide or beclomethasone or beclometasone or ciclesonide or fluticasone or flunisolide or triamcinolone or mometasone).ti,ab,kf.

25.	((glucocorticosteroid* or glucocorticoid* or corticosteroid* or cocorticoid* or corticoid* or steroid* or preventer) adj2 inhale*).ti,ab,kf.
26.	ICS.ti,ab.
27.	(Asmabec or Clenil Modulite or Qvar or Alvesco or Pulmicort or Flixotide or Novolizer or Asmanex or Aerobid or Flovent or Becotide).ti,ab,kf.
28.	*ipratropium bromide plus salbutamol/ or *budesonide plus formoterol/ or *fluticasone propionate plus salmeterol/ or *formoterol fumarate plus mometasone furoate/
29.	((combination or MART) adj2 inhaler*).ti,ab,kf.
30.	(("maintenance and reliever" or MART or SMART) adj2 (therap* or treatment*)).ti,ab,kf.
31.	(Fostair or Seretide or DuoResp or Symbicort or Relvar or Fobumix or Ventide or Aerocort).ti,ab,kf.
32.	*leukotriene receptor blocking agent/
33.	(leukotriene receptor antagonist* or leukotriene antagonist* or antileukotriene* or anti leukotriene* or leukotriene modifier* or leukotriene inhibitor* or LTRA or LTRAs).ti,ab,kf.
34.	*zafirlukast/ or *montelukast/ or *pranlukast/
35.	(zafirlukast or montelukast or pranlukast).ti,ab,kf.
36.	(Accolate or Singulair).ti,ab,kf.
37.	or/23-36
38.	22 and 37
39.	random*.ti,ab.
40.	factorial*.ti,ab.
41.	(crossover* or cross over*).ti,ab.
42.	((doubl* or singl*) adj blind*).ti,ab.
43.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
44.	crossover procedure/
45.	single blind procedure/
46.	randomized controlled trial/
47.	double blind procedure/
48.	or/39-47
49.	Systematic Review/
50.	Meta-Analysis/
51.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
52.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
53.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
54.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
55.	(search* adj4 literature).ab.
56.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
57.	cochrane.jw.
58.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
59.	or/49-58
60.	38 and (48 or 59)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Asthma] explode all trees
#2.	asthma*:ti,ab
#3.	#1 or #2
#4.	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or eudract* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an
#5.	#3 not #4
#6.	conference:pt
#7.	#5 not #6
#8.	MeSH descriptor: [Budesonide] explode all trees
#9.	MeSH descriptor: [Beclomethasone] explode all trees
#10.	MeSH descriptor: [Fluticasone] explode all trees
#11.	MeSH descriptor: [Mometasone Furoate] explode all trees
#12.	(budesonide or beclomethasone or beclometasone or ciclesonide or fluticasone or flunisolide or triamcinolone or mometasone):ti,ab
#13.	((glucocorticosteroid* or glucocorticoid* or corticosteroid* or cocorticoid* or corticoid* or steroid* or preventer) near/2 inhale*):ti,ab
#14.	ICS:ti,ab
#15.	(Asmabec or Clenil Modulite or Qvar or Alvesco or Pulmicort or Flixotide or Novolizer or Asmanex or Aerobid or Flovent or Becotide):ti,ab
#16.	MeSH descriptor: [Budesonide, Formoterol Fumarate Drug Combination] explode all trees
#17.	MeSH descriptor: [Fluticasone-Salmeterol Drug Combination] explode all trees
#18.	MeSH descriptor: [Mometasone Furoate, Formoterol Fumarate Drug Combination] explode all trees
#19.	((combination or MART) near/2 inhaler*):ti,ab
#20.	(("maintenance and reliever" or MART or SMART) near/2 (therap* or treatment*)):ti,ab
#21.	(Fostair or Seretide or DuoResp or Symbicort or Relvar or Fobumix or Ventide or Aerocort):ti,ab
#22.	MeSH descriptor: [Leukotriene Antagonists] explode all trees
#23.	(leukotriene receptor antagonist* or leukotriene antagonist* or antileukotriene* or anti leukotriene* or leukotriene modifier* or leukotriene inhibitor* or LTRA or LTRAs):ti,ab
#24.	(zafirlukast or montelukast or pranlukast):ti,ab
#25.	(Accolate or Singulair):ti,ab
#26.	(or #8-#25)
#27.	#7 and #26

Epistemonikos search terms

1.	(title:(budesonide OR beclomethasone OR beclometasone OR ciclesonide OR fluticasone OR flunisolide OR triamcinolone OR mometasone) OR abstract:(budesonide OR beclomethasone OR beclometasone OR ciclesonide OR fluticasone OR flunisolide OR triamcinolone OR mometasone)) OR (title:((glucocorticosteroid* OR glucocorticoid* OR corticosteroid* OR cocorticoid* OR

	corticoid* OR steroid* OR preventer) AND inhale) OR abstract:((glucocorticosteroid* OR glucocorticoid* OR corticosteroid* OR cocorticoid* OR corticoid* OR steroid* OR preventer) AND inhale)) OR (title:(leukotriene receptor antagonist* OR leukotriene antagonist* OR antileukotriene* OR anti leukotriene* OR leukotriene modifier* OR leukotriene inhibitor* OR LTRA OR LTRAs) OR abstract:(leukotriene receptor antagonist* OR leukotriene antagonist* OR antileukotriene* OR anti leukotriene* OR leukotriene modifier* OR leukotriene inhibitor* OR LTRA OR LTRAs)) OR (title:(zafirlukast OR montelukast OR pranlukast) OR abstract:(zafirlukast OR montelukast OR pranlukast)) AND (title:(asthma*) OR abstract:(asthma*))

B.2 Health economic literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Asthma population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies and modelling.

Table 14: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 Dec 2023	
	Modelling 1946 – 29 Dec 2023	
Embase (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 Dec 2023	
	Modelling 1974 – 29 Dec 2023	

Database	Dates searched	Search filters and limits applied
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 Dec 2023	English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	quality-adjusted life years/
25.	sickness impact profile/
26.	(quality adj2 (wellbeing or well being)).ti,ab.
27.	sickness impact profile.ti,ab.

28.	disability adjusted life.ti,ab.
29.	(qal* or qtime* or qwb* or daly*).ti,ab.
30.	(euroqol* or eq5d* or eq 5*).ti,ab.
31.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
32.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
33.	(hui or hui1 or hui2 or hui3).ti,ab.
34.	(health* year* equivalent* or hye or hyes).ti,ab.
35.	discrete choice*.ti,ab.
36.	rosser.ti,ab.
37.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
38.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
39.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
40.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
41.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
42.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
43.	or/24-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	Economics/
55.	Value of life/
56.	exp "Costs and Cost Analysis"/
57.	exp Economics, Hospital/
58.	exp Economics, Medical/
59.	Economics, Nursing/
60.	Economics, Pharmaceutical/
61.	exp "Fees and Charges"/
62.	exp Budgets/
63.	budget*.ti,ab.
64.	cost*.ti.
65.	(economic* or pharmaco?economic*).ti.
66.	(price* or pricing*).ti,ab.

67.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
68.	(financ* or fee or fees).ti,ab.
69.	(value adj2 (money or monetary)).ti,ab.
70.	or/54-69
71.	23 and 43
72.	23 and 53
73.	23 and 70

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	quality adjusted life year/
24.	"quality of life index"/
25.	short form 12/ or short form 20/ or short form 36/ or short form 8/
26.	sickness impact profile/
27.	(quality adj2 (wellbeing or well being)).ti,ab.
28.	sickness impact profile.ti,ab.
29.	disability adjusted life.ti,ab.
30.	(qal* or qtime* or qwb* or daly*).ti,ab.

31.	(euroqol* or eq5d* or eq 5*).ti,ab.
32.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
33.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
34.	(hui or hui1 or hui2 or hui3).ti,ab.
35.	(health* year* equivalent* or hye or hyes).ti,ab.
36.	discrete choice*.ti,ab.
37.	rosser.ti,ab.
38.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
39.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
40.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
41.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
42.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
43.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
44.	or/23-43
45.	statistical model/
46.	exp economic aspect/
47.	45 and 46
48.	*theoretical model/
49.	*nonbiological model/
50.	stochastic model/
51.	decision theory/
52.	decision tree/
53.	monte carlo method/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
57.	or/47-56
58.	health economics/
59.	exp economic evaluation/
60.	exp health care cost/
61.	exp fee/
62.	budget/
63.	funding/
64.	budget*.ti,ab.
65.	cost*.ti.
66.	(economic* or pharmaco?economic*).ti.
67.	(price* or pricing*).ti,ab.
68.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.

69.	(financ* or fee or fees).ti,ab.
70.	(value adj2 (money or monetary)).ti,ab.
71.	or/58-70
72.	22 and 44
73.	22 and 57
74.	22 and 71

NHS EED and HTA (CRD) search terms

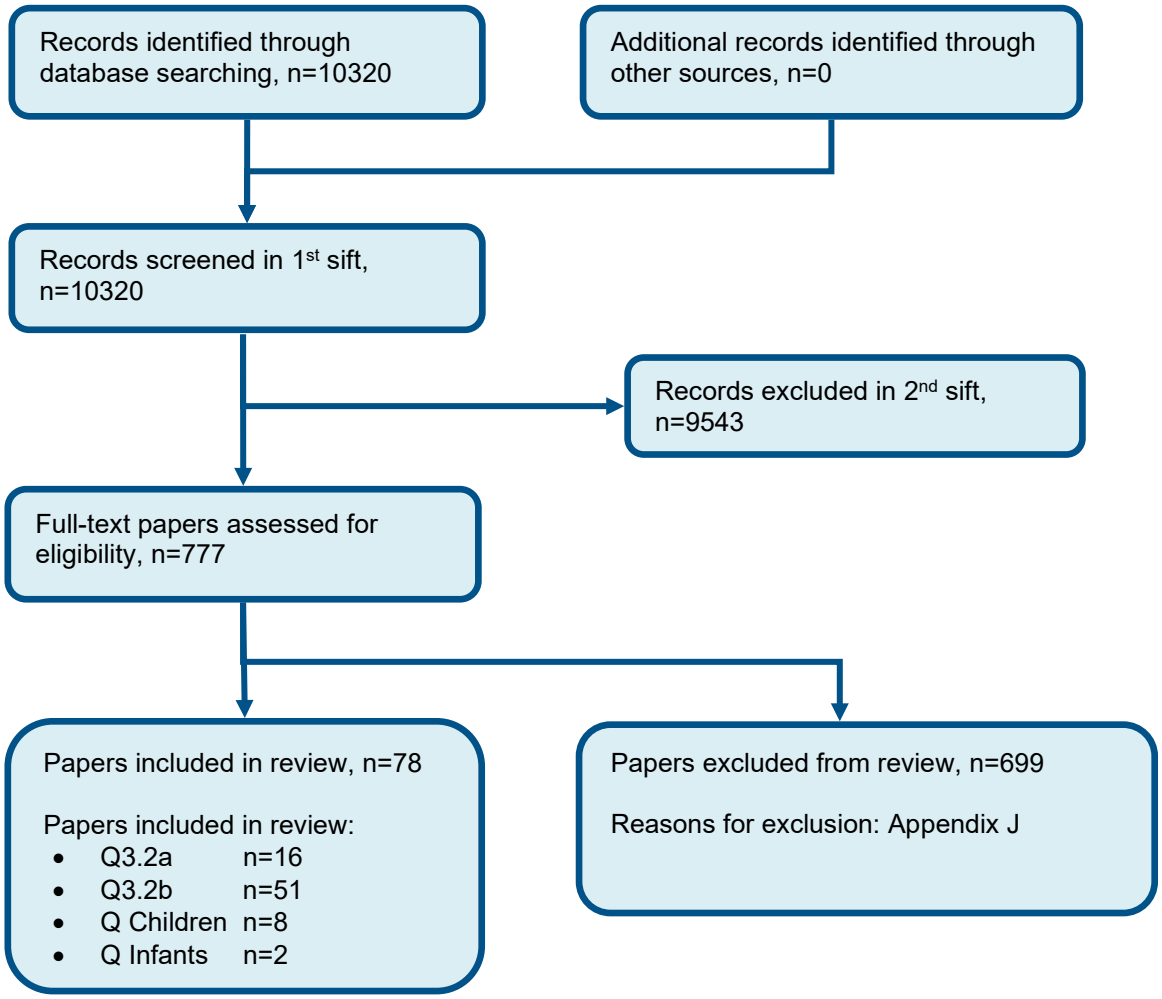
#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

INAHTA search terms

1.	(Asthma)[mh] OR (asthma*)[Title] OR (asthma*)[abs]

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of pharmacological management of asthma (drug combination and sequencing)



Appendix D – Effectiveness evidence

D.1 First add-on treatment for adults and young people aged ≥12 years with uncontrolled asthma

Atienza, 2013

Bibliographic Reference	Atienza, Tito; Aquino, Teresita; Fernandez, Marcelo; Boonsawat, Watchara; Kawai, Mitsuru; Kudo, Takahide; Ekelund, Jan; Ivanov, Stefan; Carlsson, Lars-Goran; Budesonide/formoterol maintenance and reliever therapy via Turbuhaler versus fixed-dose budesonide/formoterol plus terbutaline in patients with asthma: phase III study results.; Respirology (Carlton, Vic.); 2013; vol. 18 (no. 2); 354-63

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00839800
Study type	Randomised controlled trial (RCT)
Study location	International

Study setting	No additional information
Study dates	Not reported
Sources of funding	Funded by AstraZeneca
Inclusion criteria	Aged ≥16 years Diagnosis of asthma and ≥6 months of persistent asthma FEV1 ≥50% of predicted Reversible airway obstruction (≥12% increase in FEV1) Receiving regular ICS for ≥3 months and at a constant dose for ≥4 weeks prior to study entry At least one exacerbation in the 12 months pre-study To be randomised, participants had to use as-needed medication on ≥5 out of 7 days of the run-in Provided peak flow values for ≥8 of the last 10 days
Exclusion criteria	Respiratory infection affecting asthma within 4 weeks of study entry Treatment with oral corticosteroids within 4 weeks of study entry Current or previous smoker with a smoking history of ≥10 pack years ≥10 as needed inhalations on any single day of the run-in Exacerbation during the run-in
Recruitment / selection of participants	Method not reported

Intervention(s)	Following a 2-week run-in period (participants used their ICS at the same dose as previous treatment and terbutaline as reliever medication), participants randomised to the intervention arm received budesonide/formoterol 160/4.5 mg, one inhalation twice daily plus budesonide/ formoterol 160/4.5 mg as-needed . A maximum of 10 inhalations of as-needed medication were permitted each day. All drugs were delivered via Turbuhaler inhalers.
Population subgroups	**Exacerbations** Yes - exacerbation in past year is an inclusion criteria **Atopy** Not reported
Comparator	Participants in the comparator arm received budesonide/formoterol 160/4.5 mcg twice daily plus terbutaline 0.4 mg as needed. A maximum of 10 inhalations of as-needed medication were permitted each day. All drugs were delivered via Turbuhaler inhalers.
Number of participants	3209 enrolled 2091 randomised 1049 received regular ICS/Form + as needed, 956 completed 1042 received regular ICS/Form + SABA as needed, 932 completed
Duration of follow-up	12 months
Indirectness	Downgraded by one increment due to population indirectness - participants were receiving moderate-dose ICS at baseline, not low-dose as specified
Additional comments	ITT

Study arms

Low dose ICS/formoterol MART (N = 1049)
160/4.5 mcg BUD/FORM twice daily plus as needed

Regular low dose ICS/LABA (N = 1042)
160/4.5 BUD/FORM twice daily plus 0.4 mg terbutaline as needed

Characteristics

Arm-level characteristics

Characteristic	Low dose ICS/formoterol MART (N = 1049)	Regular low dose ICS/LABA (N = 1042)
% Female Sample size	n = 722 ; % = 69	n = 692 ; % = 66
Mean age (SD) Mean (SD)	45.7 (14.5)	45.6 (14.5)
Asian Sample size	n = 652 ; % = 62	n = 650 ; % = 62
White Sample size	n = 332 ; % = 32	n = 332 ; % = 32
Other Sample size	n = 65 ; % = 6	n = 60 ; % = 6
Comorbidities	NR	NR

Characteristic	Low dose ICS/formoterol MART (N = 1049)	Regular low dose ICS/LABA (N = 1042)
Nominal		
Lung function (% of predicted) FEV1 Mean (SD)	70.18 (14.65)	69.64 (13.75)
ICS dose Mean (SD)	662.2 (208.5)	659.2 (208.7)
Asthma control (Inhalations per day) SABA use Mean (SD)	2.41 (1.55)	2.43 (1.58)

Outcomes

Study timepoints

- Baseline
- 52 week

Continuous Outcomes

Outcome	Low dose ICS/formoterol MART, Baseline, N = 1049	Low dose ICS/formoterol MART, 52 week, N = 1049	Regular low dose ICS/LABA, Baseline, N = 1042	Regular low dose ICS/LABA, 52 week, N = 1042
Asthma control (Asthma Control Questionnaire) Final values, scale range: 0-6	1.85 (0.91)	1.16 (0.78)	1.86 (0.9)	1.29 (0.75)

Outcome	Low dose ICS/formoterol MART, Baseline, N = 1049	Low dose ICS/formoterol MART, 52 week, N = 1049	Regular low dose ICS/LABA, Baseline, N = 1042	Regular low dose ICS/LABA, 52 week, N = 1042
Mean (SD)				

Asthma control (Asthma Control Questionnaire) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Low dose ICS/formoterol MART, Baseline, N = 1049	Low dose ICS/formoterol MART, 52 week, N = 1049	Regular low dose ICS/LABA, Baseline, N = 1042	Regular low dose ICS/LABA, 52 week, N = 1042
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 170 ; % = 18	n = NA ; % = NA	n = 229 ; % = 25
Mortality Final values No of events	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0
Hospital admissions Final values No of events	n = NA ; % = NA	n = 11 ; % = 1	n = NA ; % = NA	n = 33 ; % = 3
Adverse events Final values No of events	n = NA ; % = NA	n = 602 ; % = 57	n = NA ; % = NA	n = 599 ; % = 58

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better

Hospital admissions - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Contrast Outcomes

Outcome	Low dose ICS/formoterol MART vs Regular low dose ICS/LABA, Baseline, N2 = 1026, N1 = 1034	Low dose ICS/formoterol MART vs Regular low dose ICS/LABA, 52 week, N2 = 1026, N1 = 1034
Reliever/rescue medication use (Puffs per day) Mean (95% CI)	NA (NA to NA)	-0.25 (-0.36 to -0.15)
Lung function (PEF) (Litres per minute) Mean (95% CI)	NA (NA to NA)	5.8 (2.1 to 9.5)
Lung Function (FEV1) (Litres) Mean (95% CI)	NA (NA to NA)	0.04 (0.015 to 0.064)
Severe exacerbation rate Per person year Relative risk/95% CI	NA (NA to NA)	0.71 (0.6 to 0.83)
Reliver/rescue medication use (SABA-free days) (%) Change scores Mean (95% CI)	NA (NA to NA)	4.4 (1.6 to 7.3)

Reliever/rescue medication use - Polarity - Lower values are better
Lung function (PEF) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better
Severe exacerbation rate - Polarity - Lower values are better

Reliver/rescue medication use (SABA-free days) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes – Asthma control (Asthma Control Questionnaire) – Mean (SD) - Regular ICS/formoterol + as-needed ICS/formoterol-Regular low-dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - Regular ICS/formoterol + as-needed ICS/formoterol - Regular low-dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Mortality – No Of Events - Regular ICS/formoterol + as-needed ICS/formoterol - Regular low-dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Hospital admissions – No Of Events - Regular ICS/formoterol + as-needed ICS/formoterol-Regular low-dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular ICS/formoterol + as-needed ICS/formoterol - Regular low-dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes - Reliever/rescue medication use – Mean (95% CI) - Low dose ICS/formoterol MART-Regular low dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Lung function (PEF) – Mean (95% CI) - Low dose ICS/formoterol MART - Regular low dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Lung Function (FEV1) – Mean (95% CI) - Low dose ICS/formoterol MART-Regular low dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Severe exacerbation rate – Relative Risk (95% CI) - Low dose ICS/formoterol MART-Regular low dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes - Reliever/rescue medication use (SABA-free days) – Mean (95% CI) - Low dose ICS/formoterol MART-Regular low dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Bailey, 2008

Bibliographic Reference	Bailey, William; Castro, Mario; Matz, Jonathan; White, Martha; Dransfield, Mark; Yancey, Steve; Ortega, Hector; Asthma exacerbations in African Americans treated for 1 year with combination fluticasone propionate and salmeterol or fluticasone propionate alone.; Current medical research and opinion; 2008; vol. 24 (no. 6); 1669-82

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT001102765
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	African American 12-65 years of age

	Persistent asthma for ≥6 months FEV1 60-90% of predicted ≥12% FEV1 reversibility following SABA Symptomatic whilst receiving low dose ICS (200 mcg FP or equivalent) SABA use and symptom score ≥2 on ≥4 of 7 days during the run-in period
Exclusion criteria	Exacerbation during the run-in period
Recruitment / selection of participants	Recruited from 59 centres, method not reported
Intervention(s)	Following a 4-week run-in period where participants received 250 mcg fluticasone propionate twice daily, those allocated to the intervention received 50/100 mcg salmeterol/fluticasone propionate twice per day via a Diskus inhaler. Albuterol was provided throughout the trial for use as-needed for symptom relief.
Population subgroups	**Exacerbations** Not reported **Atopy** Mixed (77% atopic in ICS/LABA group, 78% in ICS group)

Comparator	Following a 4-week run-in period where participants received 250 mcg fluticasone propionate twice daily, those allocated to the comparator received 100 mcg fluticasone propionate twice per day via a Diskus inhaler. Albuterol was provided throughout the trial for use as-needed for symptom relief.
Number of participants	475 randomised 239 allocated to ICS/LABA, 169 completed 236 allocated to ICS, 151 completed
Duration of follow-up	52 weeks
Indirectness	Some concerns due to population indirectness - entry to randomised treatment period was dependent upon gaining asthma control during the run-in period whilst receiving twice daily 250 mcg fluticasone propionate. Population therefore may not be representative of a group with asthma that is uncontrolled upon initiation of randomised treatment.
Additional comments	ITT

Study arms

Regular low dose ICS/LABA (N = 239)

50/100 mcg salmeterol/fluticasone propionate twice per day

Regular low dose ICS (N = 236)

100 mcg fluticasone propionate twice per day

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 239)	Regular low dose ICS (N = 236)
% Female Sample size	n = 143 ; % = 60	n = 150 ; % = 64

Characteristic	Regular low dose ICS/LABA (N = 239)	Regular low dose ICS (N = 236)
Mean age (SD) Range	12 to 61	12 to 63
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	77.8 (9)	77.9 (9.5)
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 52 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 239	Regular low dose ICS/LABA, 52 week, N = 239	Regular low dose ICS, Baseline, N = 236	Regular low dose ICS, 52 week, N = 236
Lung Function (FEV1) (% of predicted) Change scores Mean (SD)	NA (NA)	1.62 (12.32)	NA (NA)	-1.84 (10.67)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	15.6 (53.8)	NA (NA)	1.4 (52.9)
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-0.02 (0.94)	NA (NA)	0.03 (1.04)
Reliever/rescue medication use (SABA-free days) (%) Change scores Mean (SD)	NA (NA)	0.8 (28.8)	NA (NA)	-0.5 (32.4)

Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use - Polarity - Lower values are better
Reliever/rescue medication use (SABA-free days) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 239	Regular low dose ICS/LABA, 52 week, N = 239	Regular low dose ICS, Baseline, N = 236	Regular low dose ICS, 52 week, N = 236
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 47 ; % = 20	n = NA ; % = NA	n = 54 ; % = 23
Hospital admissions (due to asthma) Final values No of events	n = NA ; % = NA	n = 2 ; % = 1	n = NA ; % = NA	n = 3 ; % = 1
Adverse events Final values No of events	n = NA ; % = NA	n = 146 ; % = 61	n = NA ; % = NA	n = 161 ; % = 68

Severe asthma exacerbations - Polarity - Lower values are better
Hospital admissions (due to asthma) - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Contrast Outcomes

Outcome	Regular low dose ICS/LABA vs Regular low dose ICS, Baseline, N2 = 236, N1 = 239	Regular low dose ICS/LABA vs Regular low dose ICS, 52 week, N2 = 236, N1 = 239
Severe exacerbation rate Per person year Relative risk/95% CI	NA (NA to NA)	0.8 (0.58 to 1.01)

Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes – Lung Function (FEV1) – Mean (SD) - Regular low dose ICS/LABA - Regular low dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and high attrition rate (33%))*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF) – Mean (SD) - Regular low dose ICS/LABA - Regular low dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and high attrition rate (33%))*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes - Reliever/rescue medication use – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and high attrition rate (33%))*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes - Reliever/rescue medication use (SABA-free days) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and high attrition rate (33%))*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations - No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and high attrition rate (33%))*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Hospital admissions (due to asthma) – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and high attrition rate (33%))*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and high attrition rate (33%))*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Severe exacerbation rate – Relative Risk (95% CI) - Regular low dose ICS/LABA-Regular low dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and high attrition rate (33%))*
Overall bias and Directness	Overall Directness	Directly applicable

Boonsawat, 2008

Bibliographic Reference	Boonsawat, Watchara; Goryachkina, Ludmila; Jacques, Loretta; Frith, Lucy; Combined salmeterol/fluticasone propionate versus fluticasone propionate alone in mild asthma : a placebo-controlled comparison.; Clinical drug investigation; 2008; vol. 28 (no. 2); 101-11

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	Primary care or hospital outpatient department
Study dates	No additional information
Sources of funding	Sponsored by GlaxoSmithKline
Inclusion criteria	Diagnosed with asthma for at least 6 months Aged 12-79 years

	Receiving SABA as a sole therapy Pre-bronchodilator PEF ≥80% predicted Daytime asthma symptom score ≥1 on 3-6 days of the past 7 days PEF reversibility ≥15% following SABA administration or mean morning PEF <85% of the post-SABA value over 7 days
Exclusion criteria	Received ICS or leukotriene antagonists within 12 weeks of the run-in period Treatment with LABAs, sodium cromoglicate, nedocromil, anticholinergic bronchodilators of methylxanthines within 2 weeks of the run-in period Respiratory tract infection within 4 weeks Acute asthma exacerbation within 12 weeks Smoking history >10 pack years Pregnant or lactating Daily symptoms, daily SABA use or emergency room treatment during run-in
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 2-week run-in period where participants received salbutamol alone, eligible participants allocated to the intervention arm received 50/100 mcg salmeterol/fluticasone propionate once per day. Salbutamol was provided for rescue use and oral prednisolone was permitted for treatment of exacerbations.
Population subgroups	**Exacerbations** Not reported

	Atopy Not reported
Comparator	Following a 2-week run-in period where participants received salbutamol alone, eligible participants allocated to the comparator arm received 100 mcg fluticasone propionate once per day. Salbutamol was provided for rescue use and oral prednisolone was permitted for treatment of exacerbations. *Study also included a placebo arm that was excluded from this review due to not containing a relevant intervention*
Number of participants	303 randomised 149 allocated to ICS/LABA, 144 completed 154 allocated to ICS, 145 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular low dose ICS/LABA (N = 149)
50/100 mcg salmeterol/fluticasone propionate combination inhaler once daily

Regular low dose ICS (N = 154)
100 mcg fluticasone propionate once daily

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 149)	Regular low dose ICS (N = 154)
% Female Sample size	n = 80 ; % = 54	n = 87 ; % = 56
Mean age (SD) Nominal	34.7	34
Mean age (SD) Range	13 to 73	12 to 68
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
PEF % predicted Mean (SD)	94.1 (14.5)	96.4 (14.9)
FEV1 % predicted Mean (SD)	94.3 (14.5)	96 (15.2)
ICS dose Nominal	NA	NA

Characteristic	Regular low dose ICS/LABA (N = 149)	Regular low dose ICS (N = 154)
Symptom free days (%) Median (range) Nominal	42.86	57.14
Symptom free days (%) Median (range) Range	14.3 to 100	14.3 to 100
SABA free days (%) Median (range) Nominal	57.14	57.14
SABA free days (%) Median (range) Range	14.3 to 100	0 to 100

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 149	Regular low dose ICS/LABA, 12 week, N = 149	Regular low dose ICS , Baseline, N = 154	Regular low dose ICS , 12 week, N = 154
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 3 ; % = 2	n = NA ; % = NA	n = 8 ; % = 6
Adverse events Final values No of events	n = NA ; % = NA	n = 49 ; % = 33	n = NA ; % = NA	n = 57 ; % = 37

Severe asthma exacerbations - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Contrast Outcomes

Outcome	Regular low dose ICS/LABA vs Regular low dose ICS , Baseline, N2 = 154, N1 = 149	Regular low dose ICS/LABA vs Regular low dose ICS , 12 week, N2 = 154, N1 = 149
Severe exacerbation rate Per person year Relative risk/95% CI	NA (NA to NA)	2.9 (0.79 to 10.72)

Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - Regular low-dose ICS/LABA-Regular low-dose ICS -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular low-dose ICS/LABA-Regular low-dose ICS -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Severe exacerbation rate – RelativeRisk (95% CI) - Regular low dose ICS/LABA-Regular low dose ICS -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Jenkins, 2017

Bibliographic Reference	Jenkins, Christine R; Eriksson, Goran; Bateman, Eric D; Reddel, Helen K; Sears, Malcolm R; Lindberg, Magnus; O'Byrne, Paul M; Efficacy of budesonide/formoterol maintenance and reliever therapy compared with higher-dose budesonide as step-up from low-dose inhaled corticosteroid treatment.; BMC pulmonary medicine; 2017; vol. 17 (no. 1); 65

Study details

Secondary publication of another included study- see primary study for details	Secondary publication of three RCTs: STEAM: Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T, Lier PA, Jorup C. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest. 2006;129:246–56. STEP: Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, Boulet LP, Naya IP, Hultquist C. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin. 2004;20:1403–18 STAY: O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekstrom T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005;171:129–36.
Other publications associated with this study included in review	Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T, Lier PA, Jorup C. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. Chest. 2006;129:246–56. Scicchitano (2004) and O'Byrne (2005) are not included in this review, but are included in review 3.2b.
Study type	Randomised controlled trial (RCT)
Sources of funding	Original trials and post-hoc analysis funded by AstraZeneca
Inclusion criteria	As specified in primary studies. Post-hoc analysis included only participants who were being treated with low-dose (<400 mcg budesonide equivalent per day and no LABA) ICS at baseline.
Exclusion criteria	

Intervention(s)	Participants allocated to the intervention arms received either 160/9 or 320/9 mcg budesonide/formoterol, administered once per day plus up to 10 additional inhalations as-needed for symptom relief.
Comparator	Participants allocated to the comparator arms received either 320 or 640 mcg budesonide per day plus up to 10 inhalations of 0.4 mg terbutaline as-needed for symptom relief.
Number of participants	1239 randomised 626 received regular plus as-needed ICS/LABA 613 received regular ICS
Indirectness	Downgraded by one increment due to comparator indirectness. Post-hoc analysis included two studies that treated participants with both moderate dose ICS, whereas this review protocol specified low-dose ICS.
Additional comments	

Study arms

Low dose ICS/formoterol MART (N = 626)

160/9 or 320/9 mcg budesonide/formoterol per day plus as-needed for symptom relief

Regular low/moderate dose ICS (N = 616)

320 or 640 mcg budesonide per day plus terbutaline as-needed for symptom relief

Characteristics

Arm-level characteristics

Characteristic	Low dose ICS/formoterol MART (N = 626)	Regular low/moderate dose ICS (N = 616)
% Female Sample size	n = 372 ; % = 59	n = 386 ; % = 63

Characteristic	Low dose ICS/formoterol MART (N = 626)	Regular low/moderate dose ICS (N = 616)
Mean age (SD) Mean (SD)	37 (15.9)	38.3 (16.5)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	73.6 (10.9)	73 (10.7)
ICS dose Mean (SD)	357.8 (70.2)	356.1 (70.8)
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 6-12 month (Data pooled from 3 studies, one 6 months and two 12 months in duration)

Continuous Outcomes

Outcome	Low dose ICS/formoterol MART, Baseline, N = 626	Low dose ICS/formoterol MART, 6-12 month, N = 626	Regular low/moderate dose ICS, Baseline, N = 613	Regular low/moderate dose ICS, 6-12 month, N = 613
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.21 (0.3)	NA (NA)	0.11 (0.3)

Lung Function (FEV1) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Low dose ICS/formoterol MART, Baseline, N = 626	Low dose ICS/formoterol MART, 6-12 month, N = 626	Regular low/moderate dose ICS, Baseline, N = 613	Regular low/moderate dose ICS, 6-12 month, N = 613
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 38 ; % = 6.1	n = NA ; % = NA	n = 72 ; % = 11.7

Severe asthma exacerbations - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

ContinuousOutcomes – Lung Function (FEV1) – Mean (SD) - Regular low dose ICS/LABA plus ICS/LABA prn-Regular low dose ICS-t6-12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - Low dose ICS/formoterol MART-Regular low/moderate dose ICS-t6-12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Kornmann, 2020

Bibliographic Reference	Kornmann, Oliver; Mucsi, Janos; Kolosa, Nadezda; Bandelli, Lorraine; Sen, Biswajit; Satlin, Lisa C; D'Andrea, Peter; Efficacy and safety of inhaled once-daily low-dose indacaterol acetate/mometasone furoate in patients with inadequately controlled asthma: Phase III randomised QUARTZ study findings.; Respiratory medicine; 2020; vol. 161; 105809

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	QUARTZ - NCT02892344
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Novaritis
Inclusion criteria	Aged 12-75 years Diagnosis of asthma for at least 3 months

	Receiving low-dose ICS with or without LABA for at least 1-month FEV1 <90% of predicted Symptomatic with an ACQ score >1.5
Exclusion criteria	None reported
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 3-week run-in period where participants received 100 mcg fluticasone propionate twice daily, those allocated to the ICS/LABA arm received 150/80 mcg indacaterol/mometasone furoate once daily
Population subgroups	**Exacerbations** Mixed - 80% with none, 18% with one, 2% with more than one in the past year **Atopy** Not reported
Comparator	Following a 3-week run-in period where participants received 100 mcg fluticasone propionate twice daily, those allocated to the ICS arm received 200 mcg mometasone furoate once daily
Number of participants	802 randomised 398 allocated to ICS/LABA, 386 completed 404 allocated to ICS, 382 completed
Duration of follow-up	12 weeks

Indirectness	None
Additional comments	ITT

Study arms

Regular low dose ICS/LABA (N = 398)
150/80 mcg indacaterol/mometasone furoate, one inhalation once daily

Regular low dose ICS (N = 404)
200 mcg mometasone furoate, one inhalation once daily

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 398)	Regular low dose ICS (N = 404)
% Female Sample size	n = 247 ; % = 62	n = 241 ; % = 61
Mean age (SD) Mean (SD)	46.1 (16.3)	45.1 (16.3)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Characteristic	Regular low dose ICS/LABA (N = 398)	Regular low dose ICS (N = 404)
Lung function (% of predicted) FEV1 Mean (SD)	73.3 (7.57)	72.2 (7.63)
Low-dose ICS Sample size	n = 177 ; % = 45	n = 167 ; % = 41
Moderate-high-dose ICS Sample size	n = 1 ; % = 0	n = 0 ; % = 0
Low-dose ICS/LABA Sample size	n = 217 ; % = 55	n = 232 ; % = 57
Moderate-high-dose ICS/LABA Sample size	n = 3 ; % = 1	n = 0 ; % = 0
Asthma control Mean (SD)	2.24 (0.4)	2.3 (0.39)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 398	Regular low dose ICS/LABA, 12 week, N = 398	Regular low dose ICS, Baseline, N = 404	Regular low dose ICS, 12 week, N = 404
Asthma Control (Asthma Control Questionnaire-7) Change scores, scale range: 0-6 Mean (SD)	NA (NA)	-0.95 (0.82)	NA (NA)	-0.73 (0.8)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	31 (39.5)	NA (NA)	3.8 (38.5)
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.23 (0.27)	NA (NA)	0.051 (0.26)

Asthma Control (Asthma Control Questionnaire-7) - Polarity - Lower values are better
Lung function (PEF) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 398	Regular low dose ICS/LABA, 12 week, N = 398	Regular low dose ICS, Baseline, N = 404	Regular low dose ICS, 12 week, N = 404
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Regular low dose ICS/LABA, Baseline, N = 398	Regular low dose ICS/LABA, 12 week, N = 398	Regular low dose ICS, Baseline, N = 404	Regular low dose ICS, 12 week, N = 404
Hospital admissions Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 129 ; % = 32	n = NA ; % = NA	n = 155 ; % = 38

Mortality - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes – Asthma Control (Asthma Control Questionnaire-7) – Mean (SD) - Regular low-dose ICS/LABA-Regular low-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and no information on adherence to study treatments)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF) – Mean (SD) - Regular low-dose ICS/LABA-Regular low-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and no information on adherence to study treatments)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1) – Mean (SD) - Regular low-dose ICS/LABA-Regular low-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and no information on adherence to study treatments)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Mortality – No Of Events - Regular low-dose ICS/LABA-Regular low-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and no information on adherence to study treatments)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Hospital admissions – No Of Events - Regular low-dose ICS/LABA-Regular low-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and no information on adherence to study treatments)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular low-dose ICS/LABA-Regular low-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and no information on adherence to study treatments)*
Overall bias and Directness	Overall Directness	Directly applicable

Kuna, 2006

Bibliographic Reference	Kuna, P; Creemers, J P H M; Vondra, V; Black, P N; Lindqvist, A; Nihlen, U; Vogelmeier, C; Once-daily dosing with budesonide/formoterol compared with twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma.; Respiratory medicine; 2006; vol. 100 (no. 12); 2151-9

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	International - Finland, Germany, Mexico, New Zealand, Norway, Poland, Russia and Sweden
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by AstraZeneca
Inclusion criteria	≥18 years of age Diagnosis of asthma for at least 6 months that was not optimally controlled whilst receiving a daily ICS dose of 200-500 mcg for at least 30 days pre-study

	FEV1 60-90% of predicted ≥12% FEV1 reversibility after receiving SABA
Exclusion criteria	Received systemic cortiosteroids within 30 days Seasonal asthma Respiratory infection within 30 days Severe cardiovascular disorder, or any other significant disease Used beta-blockers History of smoking >10 pack years Pregnant women or not using contraceptive measures Unable to use peak flow monitor or complete a diary card during the run-in
Recruitment / selection of participants	Recruited from 61 centres, method not reported
Intervention(s)	Following a 2-week run-in period where participants received 100 mcg budesonide twice daily, those allocated to the intervention received 80/4.5 mcg budesonide/formoterol (Symbicort) to be taken twice daily as either one or two inhalations. Participants were also provided with terbutaline or another SABA to be used as-needed for symptom relief. *Two study arms containing either one or two puffs per administration combined for this review due to both containing regular low dose ICS/LABA*

Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Following a 2-week run-in period where participants received 100 mcg budesonide twice daily, those allocated to the comparator received 200 mcg budesonide (Pulmicort) to be taken once daily as a single inhalation. Participants were also provided with terbutaline or another SABA to be used as-needed for symptom relief.
Number of participants	616 randomised 409 allocated to ICS/LABA, 372 completed 207 allocated to ICS, 183 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular low dose ICS/LABA (N = 409)

80/4.5 mcg budesonide/formoterol, one or two inhalations twice daily *two study arms containing either one or two inhalations combined for this review*

Regular low dose ICS (N = 207)
200 mcg budesonide one inhalation once per day

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 409)	Regular low dose ICS (N = 207)
% Female Sample size	n = 250 ; % = 61	n = 116 ; % = 56
Mean age (SD) Nominal	44.8	45.1
Mean age (SD) Range	18 to 80	18 to 78
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Nominal	78.6	78.3
Lung function (% of predicted) FEV1 Range	23 to 123	38 to 119

Characteristic	Regular low dose ICS/LABA (N = 409)	Regular low dose ICS (N = 207)
ICS dose (mcg/day) Nominal	367	368
ICS dose (mcg/day) Range	200 to 500	200 to 500
Asthma control (%) Symptom free days Nominal	36.9	38.1
Asthma control (%) Symptom free days Range	0 to 100	0 to 100

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 409	Regular low dose ICS/LABA, 12 week, N = 409	Regular low dose ICS, Baseline, N = 207	Regular low dose ICS, 12 week, N = 207
Reliever/rescue medication use (reliever free days) (%) Final values Mean (SD)	NR (NR)	64.1 (26.5)	NR (NR)	55.5 (26.1)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	23.8 (37.8)	NA (NA)	5.5 (37.8)

Reliever/rescue medication use (reliever free days) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 409	Regular low dose ICS/LABA, 12 week, N = 409	Regular low dose ICS, Baseline, N = 207	Regular low dose ICS, 12 week, N = 207
Pneumonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 55 ; % = 15	n = NA ; % = NA	n = 25 ; % = 12
Adverse events Final values No of events	n = NA ; % = NA	n = 72 ; % = 18	n = NA ; % = NA	n = 30 ; % = 16

Pneumonia (respiratory tract infections) - Polarity - Lower values are better

Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes - Reliever/rescue medication use (reliever free days) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Pneumonia (respiratory tract infections) – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Indirectly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Lalloo, 2003

Bibliographic Reference	Lalloo, Umesh G; Malolepszy, Joseph; Kozma, Dezso; Krofta, Kamil; Ankerst, Jaro; Johansen, Bjorn; Thomson, Neil C; Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma.; Chest; 2003; vol. 123 (no. 5); 1480-7

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	International - Czech Republic, Hungary, Norway, Poland, South Africa, Sweden and the UK
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by AstraZeneca
Inclusion criteria	≥18 years of age

	Diagnosed with asthma for at least 6 months FEV1 60-90% of predicted ≥12% FEV1 reversibility after receiving SABA Using ICS at a constant dose of 200-500 mcg per day for at least one month Females required to be postmenopausal, surgically sterile or using adequate contraception
Exclusion criteria	Use of systemic corticosteroids within a month Respiratory infection affecting disease control within a month Severe cardiovascular or other concomitant disease Current and previous smokers with a history >10 pack years
Recruitment / selection of participants	Recruited from 51 centres, method not reported
Intervention(s)	Following a 2-week run-in period where participants received 100 mcg budesonide twice daily, those randomised to the intervention received 80/4.5 budesonide/formoterol twice daily. Participants also received terbutaline or salbutamol to be used as-needed for symptom relief.
Population subgroups	**Exacerbations** Not reported

	Atopy Not reported
Comparator	Following a 2-week run-in period where participants received 100 mcg budesonide twice daily, those randomised to the comparator received 200 mcg budesonide twice daily. Participants also received terbutaline or salbutamol to be used as-needed for symptom relief.
Number of participants	467 randomised 230 allocated to ICS/LABA, 215 completed 237 allocated to ICS, 215 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular low dose ICS/LABA (N = 230)
80/4.5 mcg budesonide/formoterol twice daily

Regular low dose ICS (N = 237)
200 mcg budesonide twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 230)	Regular low dose ICS (N = 237)
% Female Sample size	n = 128 ; % = 56	n = 139 ; % = 59
Mean age (SD) Nominal	42	40
Mean age (SD) Range	18 to 77	18 to 78
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Nominal	82	81
Lung function (% of predicted) FEV1 Range	38 to 117	42 to 157
ICS dose Nominal	386	387

Characteristic	Regular low dose ICS/LABA (N = 230)	Regular low dose ICS (N = 237)
ICS dose Range	200 to 500	200 to 500
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 230	Regular low dose ICS/LABA, 12 week, N = 230	Regular low dose ICS, Baseline, N = 237	Regular low dose ICS, 12 week, N = 237
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 16 ; % = 7	n = NA ; % = NA	n = 17 ; % = 7
Pneumonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 37 ; % = 16	n = NA ; % = NA	n = 40 ; % = 17

Severe asthma exacerbations - Polarity - Lower values are better
Pneumonia (respiratory tract infections) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Pneumonia (respiratory tract infections) – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Indirectly applicable

Murray, 2004

Bibliographic Reference	Murray, John; Rosenthal, Richard; Somerville, Laura; Blake, Kathryn; House, Karen; Baitinger, Leslie; VanderMeer, Anna; Dorinsky, Paul; Fluticasone propionate and salmeterol administered via Diskus compared with salmeterol or fluticasone propionate alone in patients suboptimally controlled with short-acting beta2-agonists.; Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology; 2004; vol. 93 (no. 4); 351-9

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	≥12 years of age Asthma for ≥6 months

	Treated with SABA for ≥1 month FEV1 40-85% of predicted Bronchial reversibility ≥15% following SABA Required 12 or more puffs of rescue albuterol during the 7 days preceding randomization or total symptom score of 7 or higher during this 7-day period - symptom scores were based on a 0-5 scale that described any asthma-related symptom during the previous night and day, where 0 indicates no symptoms and 5 indicates symptoms so severe that the patient could not go to work or perform normal daily activities
Exclusion criteria	Pregnant or lactating Life threatening asthma Hospitalisation due to asthma more than twice in the past year >10 pack years smoking history Significant concurrent disease Recent respiratory tract infection
Recruitment / selection of participants	Recruited from 33 centres, method not reported
Intervention(s)	Following a 2-week run-in period where participants received albuterol as-needed for symptom relief, those randomised to the intervention received 100 mcg fluticasone propionate and 50 mcg salmeterol, both taken twice daily *Study also included an arm containing salmeterol as a monotherapy, excluded from this review due to not containing a relevant intervention*

Population subgroups	**Exacerbations** Mixed **Atopy** Not reported
Comparator	Following a 2-week run-in period where participants received albuterol as-needed for symptom relief, those randomised to the comparator received 100 mcg fluticasone propionate, taken twice daily
Number of participants	177 randomised 88 allocated to ICS/LABA, 76 completed 89 allocated to ICS, 78 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular low dose ICS/LABA (N = 88)

100/50 mcg fluticasone propionate/salmeterol twice daily

Regular low dose ICS (N = 89)
100 mcg fluticasone propionate twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 88)	Regular low dose ICS (N = 89)
% Female Sample size	n = 47 ; % = 53	n = 44 ; % = 49
Mean age (SD) Nominal	36	32
Mean age (SD) Range	12 to 73	12 to 64
White Sample size	n = 63 ; % = 72	n = 75 ; % = 84
Black Sample size	n = 17 ; % = 19	n = 10 ; % = 11
Other Sample size	n = 8 ; % = 9	n = 4 ; % = 5
Comorbidities Nominal	NR	NR

Characteristic	Regular low dose ICS/LABA (N = 88)	Regular low dose ICS (N = 89)
Lung function (% of predicted) FEV1 Nominal	66	65
ICS dose Nominal	NA	NA
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA , Baseline, N = 88	Regular low dose ICS/LABA , 12 week, N = 88	Regular low dose ICS , Baseline, N = 89	Regular low dose ICS , 12 week, N = 89
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-2.8 (2.9)	NA (NA)	-1.8 (2.2)

Outcome	Regular low dose ICS/LABA , Baseline, N = 88	Regular low dose ICS/LABA , 12 week, N = 88	Regular low dose ICS , Baseline, N = 89	Regular low dose ICS , 12 week, N = 89
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.51 (0.47)	NA (NA)	0.5 (0.47)
Lung function (PEF) (% of predicted) Change scores Mean (SD)	NA (NA)	14.4 (12.2)	NA (NA)	7.6 (10.8)

Reliever/rescue medication use - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA , Baseline, N = 88	Regular low dose ICS/LABA , 12 week, N = 88	Regular low dose ICS , Baseline, N = 89	Regular low dose ICS , 12 week, N = 89
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 4 ; % = 5	n = NA ; % = NA	n = 1 ; % = 1

Severe asthma exacerbations - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes - Reliever/rescue medication use – Mean (SD) - Regular low dose ICS/LABA -Regular low dose ICS - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Missing data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1) – Mean (SD) - Regular low dose ICS/LABA -Regular low dose ICS -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Missing data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF) – Mean (SD) - Regular low dose ICS/LABA -Regular low dose ICS -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Missing data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - Regular low dose ICS/LABA -Regular low dose ICS -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Missing data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Nathan, 2012

Bibliographic Reference	Nathan, Robert A; D'Urzo, Anthony; Blazhko, Viktor; Kaiser, Kirsten; Safety and efficacy of fluticasone/formoterol combination therapy in adolescent and adult patients with mild-to-moderate asthma: a randomised controlled trial.; BMC pulmonary medicine; 2012; vol. 12; 67

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00393991
Study type	Randomised controlled trial (RCT)
Study location	International - USA, Canada and Ukraine
Study setting	No additional information
Study dates	No additional information
Sources of funding	Sponsored by SkyePharma
Inclusion criteria	≥12 years of age Diagnosed with asthma for ≥12 months

	Documented history of ICS use for ≥4 weeks at a daily dose <500 mcg fluticasone propionate, or not on ICS for ≥12 weeks pre-screening FEV1 60-85% of predicted at screening and baseline Demonstrated FEV1 reversibility (>14.5% increase following SABA) within 12 months Satisfactory inhaler technique and use of the telephone diary system ≥2 SABA uses and day/night time asthma symptoms on ≥3 out of 7 consecutive days during run-in period
Exclusion criteria	History of life-threatening asthma within 12 months Systemic corticosteroid use within 3 months or omalizumab within 6 months, leukotriene antagonist within a week Significant non-reversible pulmonary disease Respiratory tract infection within 4 weeks Smoking history >10 pack years Received β-blockers, tricyclic antidepressants, monoamine oxidase inhibitors, quinidine-type antiarrhythmics, or drugs known to inhibit CYP3A4, within a week
Recruitment / selection of participants	Recruited from 59 centres, method not reported

Intervention(s)	Following a 2-4 week run-in period (2 weeks for those on ICS, receiving 50 mcg FP twice daily, 2-4 for those on SABA alone, receiving no controller medication), eligible participants allocated to the intervention received two inhalers. The first contained 50/5 mcg fluticasone propionate/formoterol, and the other contained placebo, both of which were inhaled two times, twice daily. *Study also included arms containing formoterol monotherapy and placebo, excluded from this review due to not containing relevant interventions*
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Following a 2-4 week run-in period (2 weeks for those on ICS, receiving 50 mcg FP twice daily, 2-4 for those on SABA alone, receiving no controller medication), eligible participants allocated to the comparator received two inhalers. The first contained 50 mcg fluticasone propionate/formoterol, and the other contained placebo, both of which were inhaled two times, twice daily.
Number of participants	237 randomised 118 allocated to ICS/LABA, 99 completed 119 allocated to ICS, 97 completed
Duration of follow-up	3 months

Indirectness	None
Additional comments	ITT and per protocol

Study arms

Regular low dose ICS/LABA (N = 115)
100/10 mcg fluticasone propionate/formoterol twice daily

Regular low dose ICS (N = 117)
100 mcg fluticasone propionate twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 115)	Regular low dose ICS (N = 117)
% Female Sample size	n = 72 ; % = 63	n = 71 ; % = 61
Mean age (SD) Mean (SD)	39.8 (14.5)	38.3 (14.5)
White/Caucasian Sample size	n = 89 ; % = 77	n = 88 ; % = 75
Black Sample size	n = 13 ; % = 11	n = 16 ; % = 14
Asian	n = 6 ; % = 5	n = 4 ; % = 3

Characteristic	Regular low dose ICS/LABA (N = 115)	Regular low dose ICS (N = 117)
Sample size		
Hispanic Sample size	n = 6 ; % = 5	n = 8 ; % = 7
Other Sample size	n = 1 ; % = 1	n = 1 ; % = 1
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	73.2 (7.5)	73.5 (8.1)
Steroid free Sample size	n = 59 ; % = 51	n = 60 ; % = 51
Steroid requiring Sample size	n = 56 ; % = 49	n = 57 ; % = 49
ICS monotherapy Sample size	n = 31 ; % = 27	n = 39 ; % = 33
ICS/LABA Sample size	n = 25 ; % = 22	n = 18 ; % = 15

Characteristic	Regular low dose ICS/LABA (N = 115)	Regular low dose ICS (N = 117)
Asthma control (%) Asthma control days (last 7 days) Mean (SD)	12.8 (20.1)	14.3 (22.6)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 115	Regular low dose ICS/LABA, 12 week, N = 115	Regular low dose ICS , Baseline, N = 117	Regular low dose ICS , 12 week, N = 117
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-2.22 (1.77)	NA (NA)	-1.64 (1.74)
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.2 (0.41)	NA (NA)	0.092 (0.4)
Reliever/rescue medication use (SABA-free days) (%) Change scores	NA (NA)	55.9 (36.4)	NA (NA)	43.3 (37.7)

Outcome	Regular low dose ICS/LABA, Baseline, N = 115	Regular low dose ICS/LABA, 12 week, N = 115	Regular low dose ICS , Baseline, N = 117	Regular low dose ICS , 12 week, N = 117
Mean (SD)				

Reliever/rescue medication use - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better
Reliever/rescue medication use (SABA-free days) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 115	Regular low dose ICS/LABA, 12 week, N = 115	Regular low dose ICS , Baseline, N = 117	Regular low dose ICS , 12 week, N = 117
Severe asthma exacerbations Final values, calculated from % reported in paper No of events	n = NA ; % = NA	n = 2 ; % = 2.6	n = NA ; % = NA	n = 3 ; % = 3.4
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 38 ; % = 32	n = NA ; % = NA	n = 47 ; % = 40

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes - Reliever/rescue medication use – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on adherence to study treatments and missing outcome data with reasons for discontinuation that were related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on adherence to study treatments and missing outcome data with reasons for discontinuation that were related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes - Reliever/rescue medication use (SABA-free days) – Mean SD - Regular low dose ICS/LABA-Regular low dose ICS -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on adherence to study treatments and missing outcome data with reasons for discontinuation that were related to participant's health status)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on adherence to study treatments and missing outcome data with reasons for discontinuation that were related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Mortality – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on adherence to study treatments and missing outcome data with reasons for discontinuation that were related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on adherence to study treatments and missing outcome data with reasons for discontinuation that were related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Nelson, 2003

Bibliographic Reference	Nelson, Harold S; Wolfe, James D; Gross, Gary; Greos, Leon S; Baitinger, Leslie; Scott, Catherine; Dorinsky, Paul; Efficacy and safety of fluticasone propionate 44 microg/salmeterol 21 microg administered in a hydrofluoroalkane metered-dose inhaler as an initial asthma maintenance treatment.; Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology; 2003; vol. 91 (no. 3); 263-9

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by GlaxoSmithKline
Inclusion criteria	≥12 years of age Diagnosed with asthma requiring pharmacotherapy for at least 6 months

	FEV1 40-85% of predicted ≥15% FEV1 reversibility following SABA Treated with SABA alone in the past month Symptom score ≥7 during the run-in period (based on a 6 point scale where 0 indicates no symptoms and 5 indicates severe symptoms that inhibit daily activities)
Exclusion criteria	None reported
Recruitment / selection of participants	Recruited from 33 centres, method not reported
Intervention(s)	Following a 2-week run-in period where participants received regular placebo and as-needed albuterol, those randomised to the intervention received 44/21 mcg fluticasone propionate/salmeterol HFA, two inhalations twice per day via an MDI, resulting in a total daily dose of 176/84 mcg. Participants also received albuterol for use as-needed for symptom relief. *Study also included an arm containing salmeterol monotherapy that was excluded from this review due to not containing a relevant intervention*
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported

Comparator	Following a 2-week run-in period where participants received regular placebo and as-needed albuterol, those randomised to the comparator received 44mcg fluticasone propionate HFA, two inhalations twice per day via an MDI, resulting in a total daily dose of 176 mcg. Participants also received albuterol for use as-needed for symptom relief.
Number of participants	192 randomised 95 allocated to ICS/LABA, 86 completed 97 allocated to ICS, 89 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Unclear analysis method

Study arms

Regular low dose ICS/LABA (N = 95)

44/21 mcg fluticasone propionate/salmeterol combination inhaler, two inhalations twice daily

Regular low dose ICS (N = 97)

44 mcg fluticasone propionate, two inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 95)	Regular low dose ICS (N = 97)
% Female Sample size	n = 46 ; % = 48	n = 46 ; % = 47

Characteristic	Regular low dose ICS/LABA (N = 95)	Regular low dose ICS (N = 97)
Mean age (SD) Nominal	29.2	33.6
Mean age (SD) Range	12 to 77	12 to 76
White Sample size	n = 76 ; % = 80	n = 75 ; % = 77
African American Sample size	n = 8 ; % = 8	n = 12 ; % = 12
Other Sample size	n = 11 ; % = 12	n = 10 ; % = 10
Comorbidities Nominal	NR	NR
Lung function (%) FEV1 Nominal	67.2	64.7
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 95	Regular low dose ICS/LABA, 12 week, N = 95	Regular low dose ICS, Baseline, N = 97	Regular low dose ICS, 12 week, N = 97
Reliever/rescue medication use (rescue free days) (%) Change scores Mean (SD)	NA (NA)	40 (43.8)	NA (NA)	26.5 (36.8)
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-2.4 (3)	NA (NA)	-1.8 (2.1)
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.69 (0.49)	NA (NA)	0.51 (0.49)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	66.5 (54.3)	NA (NA)	43 (51.9)

Outcome	Regular low dose ICS/LABA, Baseline, N = 95	Regular low dose ICS/LABA, 12 week, N = 95	Regular low dose ICS, Baseline, N = 97	Regular low dose ICS, 12 week, N = 97
Lung function (PEF) (% of predicted) Change scores Mean (SD)	NA (NA)	14.1 (11.8)	NA (NA)	8.6 (10.3)

Reliever/rescue medication use (rescue free days) - Polarity - Higher values are better
Reliever/rescue medication use - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 95	Regular low dose ICS/LABA, 12 week, N = 95	Regular low dose ICS, Baseline, N = 97	Regular low dose ICS, 12 week, N = 97
Adverse events Final values No of events	n = NA ; % = NA	n = 16 ; % = 17	n = NA ; % = NA	n = 16 ; % = 16

Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes - Reliever/rescue medication use (rescue free days) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes - Reliever/rescue medication use – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF%) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Pearlman, 2013

Bibliographic Reference	Pearlman, David S; LaForce, Craig F; Kaiser, Kirsten; Fluticasone/Formoterol combination therapy compared with monotherapy in adolescent and adult patients with mild to moderate asthma.; Clinical therapeutics; 2013; vol. 35 (no. 7); 950-66

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00394199
Study type	Randomised controlled trial (RCT)
Study location	North America
Study setting	No additional information
Study dates	June 2006 - January 2008
Sources of funding	Sponsored by SkyePharma
Inclusion criteria	Asthma diagnosis for ≥12 months If receiving ICS, dose no higher than 500 mcg fluticasone propionate per day for ≥4 weeks

	If not receiving ICS, no prior ICS use within 12 weeks FEV1 60-85% of predicted at screening and baseline ≥14.5% FEV1 reversibility following SABA ≥2 SABA inhalations on any 3 of 7 consecutive days of the run-in period At least one night with sleep disturbance or at least 3 days with symptoms during the run-in period
Exclusion criteria	Pregnant, lactating or not using birth control History of life threatening ashtma within a year (near-fatal asthma, hospitalisation, ER visit or intubation) Systemic corticosteroid use within 3 months Omalizumab use within 6 months Leukotriene antagonist use within a week Respiratory tract infection within a month Significant non-reversible pulmonary disease (COPD, cystic fibrosis, bronchiectasis) Smoking history >10 pack years

	Receiving any medication known to interfere with study medication
Recruitment / selection of participants	Recruited from 43 centres, method not reported
Intervention(s)	Following a 2-4 week run-in period, where participants receiving ICS pre-study received 50 mcg fluticasone propionate twice daily plus salbutamol as-needed, and non-steroid receiving participants received salbutamol alone, those randomised to the intervention received 50/5 mcg fluticasone propionate/formoterol, taken as two inhalations twice per day along with a placebo inhaler taken at the same time. *Study also included an arm containing formoterol monotherapy that was excluded from this review due to not containing a relevant intervention*
Population subgroups	**Exacerbations** None with a year **Atopy** Not reported
Comparator	Following a 2-4 week run-in period, where participants receiving ICS pre-study received 50 mcg fluticasone propionate twice daily plus salbutamol as-needed, and non-steroid receiving participants received salbutamol alone, those randomised to the comparator received 50 mcg fluticasone propionate, taken as two inhalations twice per day along with a placebo inhaler taken at the same time.

Number of participants	238 randomised 119 allocated to ICS/LABA, 99 completed 119 allocated to ICS, 89 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT and per protocol

Study arms

Regular low dose ICS/LABA (N = 119)

Regular low dose ICS (N = 119)

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 119)	Regular low dose ICS (N = 119)
% Female Sample size	n = 65 ; % = 55	n = 70 ; % = 59
Mean age (SD) Mean (SD)	38.1 (15.4)	36.6 (15.1)
White/Caucasian Sample size	n = 94 ; % = 79	n = 89 ; % = 75

Characteristic	Regular low dose ICS/LABA (N = 119)	Regular low dose ICS (N = 119)
Black Sample size	n = 13 ; % = 11	n = 20 ; % = 17
Asian Sample size	n = 3 ; % = 3	n = 3 ; % = 3
Hispanic Sample size	n = 8 ; % = 7	n = 7 ; % = 6
Other Sample size	n = 1 ; % = 1	n = 0 ; % = 0
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	73.6 (7.3)	73.5 (7.7)
Steroid using Sample size	n = 65 ; % = 55	n = 63 ; % = 53
Steroid free Sample size	n = 54 ; % = 45	n = 56 ; % = 47
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 119	Regular low dose ICS/LABA, 12 week, N = 119	Regular low dose ICS, Baseline, N = 119	Regular low dose ICS, 12 week, N = 119
Reliever/rescue medication use (SABA-free days) (%) Change scores Mean (SD)	NA (NA)	51.8 (37.4)	NA (NA)	39.3 (40.9)

Reliever/rescue medication use (SABA-free days) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 119	Regular low dose ICS/LABA, 12 week, N = 119	Regular low dose ICS, Baseline, N = 119	Regular low dose ICS, 12 week, N = 119
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 1 ; % = 1	n = NA ; % = NA	n = 3 ; % = 3
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Regular low dose ICS/LABA, Baseline, N = 119	Regular low dose ICS/LABA, 12 week, N = 119	Regular low dose ICS, Baseline, N = 119	Regular low dose ICS, 12 week, N = 119
Adverse events Final values No of events	n = NA ; % = NA	n = 52 ; % = 44	n = NA ; % = NA	n = 52 ; % = 44

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes - Reliever/rescue medication use (SABA-free days) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on adherence to study treatments and missing outcome data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on adherence to study treatments and missing outcome data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Mortality – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on adherence to study treatments and missing outcome data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on adherence to study treatments and missing outcome data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Pearlman, 2004

Bibliographic Reference	Pearlman, David S; Peden, David; Condemi, John J; Weinstein, Steven; White, Martha; Baitinger, Leslie; Scott, Catherine; Ho, Shu-Yen; House, Karen; Dorinsky, Paul; Efficacy and safety of fluticasone propionate/salmeterol HFA 134A MDI in patients with mild-to-moderate persistent asthma.; The Journal of asthma : official journal of the Association for the Care of Asthma; 2004; vol. 41 (no. 8); 797-806

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by GlaxoSmithKline
Inclusion criteria	Aged ≥12 years Requiring asthma pharmacotherapy for at least 6 months (stratified into ICS (beclomethasone dipropionate (252–336 mcg/day), triamcinolone acetonide (600– 800 mcg/day), flunisolide (1000 mcg/day), fluticasone propionate (176 mcg/day of

	MDI aerosol, 200 mg/day of the inhalation powder), or budesonide (400–600 mcg/ day) and bronchodilator-receiving (SABA or salmeterol)) FEV1 40-85% of predicted both at screening and at the end of the run-in ≥15% bronchial reversibility after SABA
Exclusion criteria	Receving ICS and LABA concurrently within a month >3 night awakenings due to asthma during the last 7 days of the run-in ≥12 inhalations of salbutamol on ≥3 days of the run-in for those previously receiving ICS or SABA, ≥6 inhalations for those previously receiving salmeterol Total symptom score <7 during the final week of the run-in (0 = no symptoms, 5 = severe enough to interfere with daily activities)
Recruitment / selection of participants	Recruited from 36 centres, method not reported
Intervention(s)	Following the 2-week run-in period where participants received regular placebo and salbutamol for use as-needed, those randomised to the intervention received 44/21 mcg fluticasone propionate/salmeterol HFA, taken as two inhalations twice per day via MDI, equally a total daily dose of 176/84 mcg. *Study also included two addiitonal arms containing salmeterol monotherapy and placebo that were excluded from this review due to not containing relevant interventions*
Population subgroups	**Exacerbations**

	Not reported **Atopy** Not reported
Comparator	Following the 2-week run-in period where participants received regular placebo and salbutamol for use as-needed, those randomised to the comparator received 44 mcg fluticasone propionate CFC, taken as two inhalations twice per day via MDI, equalling a total daily dose of 176 mcg.
Number of participants	181 randomised 92 allocated to ICS/LABA, 85 completed 89 allocated to ICS, 75 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT with LOCF

Study arms

Regular low dose ICS/LABA (N = 92)
88/42 mcg fluticasone propionate/salmeterol combination inhaler used twice daily

Regular low dose ICS (N = 89)
88 mcg fluticasone propionate twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 92)	Regular low dose ICS (N = 89)
% Female Sample size	n = 57 ; % = 62	n = 52 ; % = 58
Mean age (SD) Nominal	32.8	34.7
Mean age (SD) Range	12 to 63	12 to 74
Caucasian Sample size	n = 67 ; % = 73	n = 74 ; % = 83
African American Sample size	n = 17 ; % = 18	n = 9 ; % = 10
Other Sample size	n = 8 ; % = 9	n = 6 ; % = 7
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	68.1 (1.2)	67.1 (1.3)

Characteristic	Regular low dose ICS/LABA (N = 92)	Regular low dose ICS (N = 89)
ICS Sample size	n = 33 ; % = 36	n = 34 ; % = 38
Salmeterol Sample size	n = 22 ; % = 24	n = 23 ; % = 26
SABA Sample size	n = 37 ; % = 40	n = 32 ; % = 36
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 92	Regular low dose ICS/LABA, 12 week, N = 92	Regular low dose ICS, Baseline, N = 89	Regular low dose ICS, 12 week, N = 89
Reliever/rescue medication use (SABA-free days) (%) Change scores Mean (SD)	NA (NA)	42.1 (45.1)	NA (NA)	13.5 (37.7)

Outcome	Regular low dose ICS/LABA, Baseline, N = 92	Regular low dose ICS/LABA, 12 week, N = 92	Regular low dose ICS, Baseline, N = 89	Regular low dose ICS, 12 week, N = 89
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.58 (0.48)	NA (NA)	0.36 (0.47)
Lung function (PEF) (litres/minute) Change scores Mean (SD)	NA (NA)	57.8 (49.9)	NA (NA)	27.2 (50.9)

Reliever/rescue medication use (SABA-free days) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 92	Regular low dose ICS/LABA, 12 week, N = 92	Regular low dose ICS, Baseline, N = 89	Regular low dose ICS, 12 week, N = 89
Adverse events Final values No of events	n = NA ; % = NA	n = 6 ; % = 7	n = NA ; % = NA	n = 5 ; % = 6

Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes - Reliever/rescue medication use (SABA-free days) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and missing outcome data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and missing outcome data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and missing outcome data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events - No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and missing outcome data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Rabe, 2006

Bibliographic Reference	Rabe, Klaus F; Atienza, Tito; Magyar, Pal; Larsson, Per; Jorup, Carin; Lalloo, Umesh G; Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study.; Lancet (London, England); 2006; vol. 368 (no. 9537); 744-53

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	No additional information
Study dates	April 2003 - December 2004
Sources of funding	Sponsored by AstraZeneca
Inclusion criteria	Aged ≥12 years Diagnosed with asthma for ≥6 months

	>1 severe exacerbation in the past 12 months Used ICS for at least 3 months, and at a constant dose for at least 4 weeks FEV1 50-100% of predicted with ≥12% reversibility and 200 mL after receiving SABA Used reliever medication on ≥5 out of 7 days of the run-in
Exclusion criteria	Respiratory infection affecting asthma within a month Oral corticosteroid use within a month Used reliever medication >10 times on any day of the run-in
Recruitment / selection of participants	Recruited from 289 centres in 20 countries, method not reported
Intervention(s)	Following a two-week run-in period where participants received 160/4.5 mcg budesonide/formoterol, one inhalation twice per day plus 0.4 mg terbutaline as-needed, those allocated to the intervention arm continued to receive 160/4.5 mcg budesonide/formoterol, one inhalation twice per day, but started using the same inhaler as their as-needed reliever medication. Participants could use up to 10 inhalations of as-needed medication per day, beyond which they were advised to contact the study coordinator.
Population subgroups	**Exacerbations** >1 in the past year **Atopy** Not reported
Comparator	Following a two-week run-in period where participants received 160/4.5 mcg budesonide/formoterol, one inhalation twice per day plus 0.4 mg terbutaline as-needed, those allocated to the intervention arm continued to receive 160/4.5 mcg

	budesonide/formoterol, one inhalation twice per day, with 0.4 mg terbutaline used as-needed reliever medication. Participants could use up to 10 inhalations of as-needed medication per day, beyond which they were advised to contact the study coordinator. *Study also contained a study arm where participants received regular ICS/LABA with formoterol as-needed - excluded from this review as LABA is not a relevant reliever medication in isolation*
Number of participants	3394 randomised 1113 allocated to ICS/LABA + ICS/LABA, 991 completed completed 1141 allocated to ICS/LABA + SABA, 990 completed 1140 allocated to ICS/LABA + LABA (excluded from this review)
Duration of follow-up	12 months
Indirectness	Downgraded by one increment due to population indirectness - participants could have been receiving any dose of ICS at screening (average ~750 mcg per day), protocol specified low-dose ICS as pre-study treatment
Additional comments	ITT

Study arms

Low dose ICS/formoterol MART (N = 1113)

160/4.5 mcg budesonide/formoterol, one inhalation twice per day plus additional inhalations as-needed for symptom relief

Regular low dose ICS/LABA (N = 1141)

160/4.5 mcg budesonide/formoterol, one inhalation twice per day plus 0.4 mg terbutaline as-needed for symptom relief

Characteristics

Arm-level characteristics

Characteristic	Low dose ICS/formoterol MART (N = 1113)	Regular low dose ICS/LABA (N = 1141)
% Female Sample size	n = 676 ; % = 61	n = 691 ; % = 61
Mean age (SD) Mean (range) Nominal	42	43
Mean age (SD) Mean (range) Range	12 to 89	12 to 83
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) Mean (range) FEV1 Nominal	72	72
Lung function (% of predicted) Mean (range) FEV1 Range	30 to 110	39 to 100

Characteristic	Low dose ICS/formoterol MART (N = 1113)	Regular low dose ICS/LABA (N = 1141)
ICS dose Mean (range) and proportion receiving LABA at screening Nominal	757	751
ICS dose Mean (range) and proportion receiving LABA at screening Range	160 to 1600	250 to 1600
ICS dose Mean (range) and proportion receiving LABA at screening Sample size	n = 673 ; % = 59	n = 657 ; % = 59
Asthma control Mean (range) ACQ-5 score Nominal	1.9	1.9
Asthma control Mean (range) ACQ-5 score Range	0 to 4.8	0 to 4.8

Outcomes

Study timepoints

- Baseline
- 12 month

Dichotomous Outcomes

Outcome	Low dose ICS/formoterol MART, Baseline, N = 1107	Low dose ICS/formoterol MART, 12 month, N = 1107	Regular low dose ICS/LABA, Baseline, N = 1138	Regular low dose ICS/LABA, 12 month, N = 1138
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 143 ; % = 13	n = NA ; % = NA	n = 245 ; % = 22

Severe asthma exacerbations - Polarity - Lower values are better

Contrast Outcomes

Outcome	Low dose ICS/formoterol MART vs Regular low dose ICS/LABA, Baseline, N2 = 1138, N1 = 1107	Low dose ICS/formoterol MART vs Regular low dose ICS/LABA, 12 month, N2 = 1138, N1 = 1107
Asthma control (Asthma Control Questionnaire) Scale range: 0-6, change scores Mean (95% CI)	NA (NA to NA)	-0.15 (-0.21 to -0.08)
Reliever/rescue medication use (Puffs per day) Change scores Mean (95% CI)	NA (NA to NA)	-0.2 (-0.28 to -0.11)
Lung Function (FEV1) (Litres) Change scores Mean (95% CI)	NA (NA to NA)	0.08 (0.05 to 0.1)

Outcome	Low dose ICS/formoterol MART vs Regular low dose ICS/LABA, Baseline, N2 = 1138, N1 = 1107	Low dose ICS/formoterol MART vs Regular low dose ICS/LABA, 12 month, N2 = 1138, N1 = 1107
Lung function (PEF) (Litres per minute) Change scores Mean (95% CI)	NA (NA to NA)	7.5 (4.2 to 10.7)
Severe exacerbation rate Per person year Relative risk/95% CI	NA (NA to NA)	0.53 (0.45 to 0.63)

Asthma control (Asthma Control Questionnaire) - Polarity - Lower values are better
Reliever/rescue medication use - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better
Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - Regular ICS/formoterol plus ICS/formoterol as-needed-Regular low-dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Asthma control (Asthma Control Questionnaire) – Mean (95% CI) - Regular ICS/formoterol plus ICS/formoterol as-needed-Regular low-dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes - Reliever/rescue medication use – Mean (95% CI) - Regular ICS/formoterol plus ICS/formoterol as-needed-Regular low-dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Lung Function (FEV1) – Mean (95% CI) - Regular ICS/formoterol plus ICS/formoterol as-needed-Regular low-dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Lung function (PEF) – Mean (95% CI) - Regular ICS/formoterol plus ICS/formoterol as-needed-Regular low-dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Severe exacerbation rate – Relative Risk (95% CI) - Low dose ICS/formoterol MART-Regular low dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Rabe, 2006

Bibliographic Reference	Rabe, Klaus F; Pizzichini, Emilio; Stallberg, Bjorn; Romero, Santiago; Balanzat, Ana M; Atienza, Tito; Lier, Per Arve; Jorup, Carin; Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial.; Chest; 2006; vol. 129 (no. 2); 246-256

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	International - Argentina, Brazil, China, Denmark, Indonesia, Norway, the Philippines, Spain and Sweden
Study setting	No additional information
Study dates	No additional information
Sources of funding	Sponsored by AstraZeneca
Inclusion criteria	Aged 12-80 years Diagnosed with asthma for at least 6 months

	FEV1 60-100% of predicted ≥12% FEV1 increase after receiving SABA and ≥200 mL in those 18 years and older, or PEFv ≥12% on ≥3 of the last 10 days of the run-in period Receiving ICS at a dose of 200-500 mcg per day for at least 30 days ≥7 inhalations of as-needed medication during the last 10 days of the run-in period, but <10 on any single day
Exclusion criteria	Use of systemic corticosteroids or inhaled cromones within 30 days Respiratory infection affecting asthma control within 30 days Significant comorbidity or hypersensitivity to study medication Current/previous smokers with a history >10 pack years Any exacerbation during the run-in period
Recruitment / selection of participants	Recruited from 77 centres, method not reported
Intervention(s)	Following a 14-18 day run-in period where participants received 100 mcg budesonide twice daily plus salbutamol as-needed, those randomised to the intervention received 80/4.5 mcg budesonide/formoterol, two inhalations once per day plus additional inhalations as-needed for symptom relief, via a dry powdered inhaler (80 mcg budesonide corresponds to 100 mcg delivered by MDI). Participants were allowed a maximum of 10 as-needed inhalations per day. If more than 10 inhalations were needed treatment was able to be adjusted at the discretion of the investigator.

Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Following a 14-18 day run-in period where participants received 100 mcg budesonide twice daily plus salbutamol as-needed, those randomised to the comparator received 160 mcg budesonide, two inhalations once per day plus 0.4 mg terbutaline as-needed for symptom relief, via a dry powdered inhaler. Participants were allowed a maximum of 10 as-needed inhalations per day. If more than 10 inhalations were needed treatment was able to be adjusted at the discretion of the investigator.
Number of participants	697 randomised 355 allocated to regular ICS/LABA plus ICS/LABA as-needed, 328 completed 342 allocated to regular ICS, 311 completed
Duration of follow-up	6 months
Indirectness	None
Additional comments	ITT

Study arms

Low dose ICS/formoterol MART (N = 355)

80/4.5 mcg budesonide/formoterol two inhalations once daily plus additional inhalations as-needed for symptom relief

Regular low dose ICS (N = 342)
160 mcg budesonide, two inhalations once daily plus terbutaline as-needed for symptom relief

Characteristics

Arm-level characteristics

Characteristic	Low dose ICS/formoterol MART (N = 355)	Regular low dose ICS (N = 342)
% Female Sample size	n = 208 ; % = 59	n = 219 ; % = 64
Mean age (SD) Nominal	38	38
Mean age (SD) Range	12 to 79	11 to 78
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Nominal	75	75
Lung function (% of predicted) FEV1	51 to 123	52 to 109

Characteristic	Low dose ICS/formoterol MART (N = 355)	Regular low dose ICS (N = 342)
Range		
ICS dose Nominal	353	343
ICS dose Range	200 to 500	200 to 500
ICS dose Sample size	n = NA ; % = NA	n = NA ; % = NA
Receiving LABA Nominal	NA	NA
Receiving LABA Range	NA to NA	NA to NA
Receiving LABA Sample size	n = 45 ; % = 13	n = 35 ; % = 10
Receiving ICS/LABA combination Nominal	NA	NA
Receiving ICS/LABA combination Range	NA to NA	NA to NA
Receiving ICS/LABA combination Sample size	n = 36 ; % = 10	n = 26 ; % = 8

Characteristic	Low dose ICS/formoterol MART (N = 355)	Regular low dose ICS (N = 342)
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 6 month

Dichotomous Outcomes

Outcome	Low dose ICS/formoterol MART, Baseline, N = 355	Low dose ICS/formoterol MART, 6 month, N = 355	Regular low dose ICS, Baseline, N = 342	Regular low dose ICS, 6 month, N = 342
Pneumonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 53 ; % = 16	n = NA ; % = NA	n = 54 ; % = 17
Hospital admissions Final values No of events	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 10 ; % = 3
Adverse events Final values No of events	n = NA ; % = NA	n = 82 ; % = 23	n = NA ; % = NA	n = 85 ; % = 25

Pneumonia (respiratory tract infections) - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better

Adverse events - Polarity - Lower values are better

Contrast Outcomes

Outcome	Low dose ICS/formoterol MART vs Regular low dose ICS, Baseline, N2 = 342, N1 = 355	Low dose ICS/formoterol MART vs Regular low dose ICS, 6 month, N2 = 342, N1 = 355
Severe exacerbation rate Per person year Relative risk/95% CI	NA (NA to NA)	4.23 (3.64 to 4.9)
Lung function (PEF) (l/minute) Final values Mean (95% CI)	NA (NA to NA)	25 (19.4 to 30.6)
Reliever/rescue medication use (Puffs per day) Final values Mean (95% CI)	NA (NA to NA)	-0.34 (-0.51 to -0.17)
Reliever/rescue medication use (SABA-free days) (%) Final values Mean (95% CI)	NA (NA to NA)	8.1 (2.5 to 12.7)

Severe exacerbation rate - Polarity - Lower values are better
Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use - Polarity - Lower values are better
Reliever/rescue medication use (SABA-free days) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Dichotomous Outcomes – Pneumonia (respiratory tract infections) – No Of Events - Regular low dose ICS/LABA plus ICS/LABA prn-Regular low dose ICS-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable

Dichotomous Outcomes – Hospital admissions – No Of Events - Regular low dose ICS/LABA plus ICS/LABA prn-Regular low dose ICS-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular low dose ICS/LABA plus ICS/LABA prn-Regular low dose ICS-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Severe exacerbation rate – Relative Risk (95% CI) - Low dose ICS/formoterol MART-Regular low dose ICS-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Lung function (PEF) – Mean (95% CI) - Low dose ICS/formoterol MART-Regular low dose ICS-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes - Reliever/rescue medication use – Mean (95% CI) - Low dose ICS/formoterol MART-Regular low dose ICS-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes - Reliever/rescue medication use (SABA-free days) – Mean (95% CI) - Low dose ICS/formoterol MART-Regular low dose ICS-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Renzi, 2010

Bibliographic Reference	Renzi, Paolo M; Howard, Lisa A; Ortega, Hector G; Ahmad, Faiz F; Chapman, Kenneth R; Low-dose fluticasone propionate with and without salmeterol in steroid-naive patients with mild, uncontrolled asthma.; Respiratory medicine; 2010; vol. 104 (no. 4); 510-7

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Canada
Study setting	45 general practices and 15 specialist centres
Study dates	October 2002 - February 2004
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	≥12 years of age Documented history of asthma treated with SABA alone

	FEV1 ≥80% of predicted Asthma symptom score ≥2 on ≥3 days, disruption of sleep on ≥2 occasions or use of rescue medication on ≥4 days during the final 7 days of the run-in period
Exclusion criteria	Use of controller medication in the past month Systemic corticosteroid use in the past 3 months Exacerbation requiring either ER treatment within 6 weeks, or hospitalisation within 12 weeks Smoking history >10 pack years Changed asthma medication, suffered a respiratory tract infection or required an ER visit or hospitalisation during the run-in period
Recruitment / selection of participants	Recruited from general practices and specialist centres, method not reported
Intervention(s)	Following a run-in period, participants randomised to the intervention received 50/100 mcg salmeterol/fluticasone propionate, one inhalation twice per day via a Diskus inhaler. Participants also received salbutamol for use as-needed for symptom relief.
Population subgroups	**Exacerbations** None within 6 weeks **Atopy** Not reported
Comparator	Following a run-in period, participants randomised to the comparator received 100 mcg fluticasone propionate, one inhalation twice per day via a Diskus inhaler. Participants also received salbutamol for use as-needed for symptom relief.

Number of participants	516 randomised 253 allocated to ICS/LABA, 209 completed 263 allocated to ICS, 224 completed
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	ITT with LOCF

Study arms

Regular low dose ICS/LABA (N = 253)

50/100 mcg salmeterol/fluticasone propionate twice daily

Regular low dose ICS (N = 263)

100 mcg fluticasone propionate twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 253)	Regular low dose ICS (N = 263)
% Female Sample size	n = 162 ; % = 64	n = 169 ; % = 64
Mean age (SD) Mean (SE)	34.8 (0.9)	34.3 (0.9)

Characteristic	Regular low dose ICS/LABA (N = 253)	Regular low dose ICS (N = 263)
Caucasian Sample size	n = 225 ; % = 89	n = 236 ; % = 90
Black Sample size	n = 4 ; % = 2	n = 5 ; % = 2
Asian Sample size	n = 22 ; % = 9	n = 18 ; % = 7
Other Sample size	n = 2 ; % = 0	n = 4 ; % = 2
Comorbidities Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SE)	92.8 (0.7)	92.7 (0.64)
ICS dose Nominal	NA	NA
Asthma control Daily SABA inhalations Mean (SE)	1.7 (1.41)	1.6 (1.31)

Outcomes

Study timepoints

- Baseline
- 24 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 253	Regular low dose ICS/LABA, 24 week, N = 253	Regular low dose ICS, Baseline, N = 263	Regular low dose ICS, 24 week, N = 263
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-1.2 (0.6)	NA (NA)	-1 (0.6)
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.14 (0.43)	NA (NA)	0.08 (0.3)

Reliever/rescue medication use - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 253	Regular low dose ICS/LABA, 24 week, N = 253	Regular low dose ICS, Baseline, N = 263	Regular low dose ICS, 24 week, N = 263
Hospital admissions (ER visits) Final values No of events	n = NA ; % = NA	n = 3 ; % = 1	n = NA ; % = NA	n = 3 ; % = 1

Outcome	Regular low dose ICS/LABA, Baseline, N = 253	Regular low dose ICS/LABA, 24 week, N = 253	Regular low dose ICS, Baseline, N = 263	Regular low dose ICS, 24 week, N = 263
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0

Hospital admissions (ER visits) - Polarity - Lower values are better
Mortality - Polarity - Lower values are better

Contrast Outcomes

Outcome	Regular low dose ICS/LABA vs Regular low dose ICS, Baseline, N2 = 263, N1 = 253	Regular low dose ICS/LABA vs Regular low dose ICS, 24 week, N2 = 263, N1 = 253
Severe exacerbation rate Per person year Relative risk/95% CI	NA (NA to NA)	1.04 (0.21 to 5.15)

Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Continuous Outcomes - Reliever/rescue medication use – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes - Lung Function (FEV1) – Mean (SD) - Regular low dose ICS/LABA-Regular low dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Hospital admissions (ER visits) - No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Indirectly applicable

Dichotomous Outcomes – Mortality – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Severe exacerbation rate – Relative Risk (95% CI) - Regular low dose ICS/LABA-Regular low dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Strand, 2004

Bibliographic Reference	Strand, Anne Mette; Luckow, Anders; Initiation of maintenance treatment of persistent asthma: salmeterol/fluticasone propionate combination treatment is more effective than inhaled steroid alone.; Respiratory medicine; 2004; vol. 98 (no. 10); 1008-15

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Denmark
Study setting	44 general practices and 1 hospital department
Study dates	No additional information
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	≥18 years of age Diagnosis of asthma for ≥3 months that was persistent according to GINA guidelines

	Using SABA ≥1 time per week for symptom relief PEFv ≥20%, FEV1 reversibility ≥15% after SABA or PC20 methacholine ≤4 mg/mL
Exclusion criteria	Pregnant Exacerbation during the run-in period Respiratory tract infection or middle-ear infection within a month Serious cardiovascular disease, diabetes, untreated hypokalaemia or thyrotoxicosis Use of LABA, ICS or other long-acting medication within 2 months Oral or parenteral corticosteroid use within a month Unable to operate a peak flow meter or inhaler
Recruitment / selection of participants	Recruited from 45 centres, method not reported
Intervention(s)	Following a 2-week run-in period, participants allocated to the intervention received 50/100 mcg salmeterol/fluticasone propionate twice per day via a Diskus inhaler. Participants were provided with a salbutamol inhaler for use as-needed for symptom relief.
Population subgroups	**Exacerbations**

	Not reported **Atopy** Not reported
Comparator	Following a 2-week run-in period, participants allocated to the comparator received 100 mcg fluticasone propionate twice per day via a Diskus inhaler. Participants were provided with a salbutamol inhaler for use as-needed for symptom relief.
Number of participants	150 randomised 78 allocated to ICS/LABA, 67 completed 72 allocated to ICS, 59 completed
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular low dose ICS/LABA (N = 78)
50/100 mcg salmeterol/fluticasone propionate twice daily

Regular low dose ICS (N = 72)
100 mcg fluticasone propionate twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA (N = 78)	Regular low dose ICS (N = 72)
% Female Sample size	n = 40 ; % = 51	n = 45 ; % = 63
Mean age (SD) Mean (SD)	39 (15)	38 (15)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Lung function (% of predicted) PEF Mean (SD)	77 (21)	83 (18)
ICS dose Nominal	NA	NA
Asthma control Nominal	NR	NR

Outcomes

Study timepoints

- Baseline

- 24 week

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA, Baseline, N = 78	Regular low dose ICS/LABA, 24 week, N = 78	Regular low dose ICS, Baseline, N = 72	Regular low dose ICS, 24 week, N = 72
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 48 ; % = 62	n = NA ; % = NA	n = 42 ; % = 58

Severe asthma exacerbations - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Dichotomous Outcomes – Severe asthma exacerbations - No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular low dose ICS/LABA-Regular low dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

D.2 Further step-up treatment for adults and young people aged ≥12 years with uncontrolled asthma

Barnes, 2007

Bibliographic Reference	Barnes, Neil; Laviolette, Michel; Allen, David; Flood-Page, Patrick; Hargreave, Frederick; Corris, Paul; O'Connor, Brian J; Tate, Helen; Parker, Debbie; Pavord, Ian; Effects of montelukast compared to double dose budesonide on airway inflammation and asthma control.; Respiratory medicine; 2007; vol. 101 (no. 8); 1652-8

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	UK and Canada
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by Merck, Sharp and Dohme Ltd
Inclusion criteria	Non-smokers 15-70 years old

	Asthma symptoms for >1 year Currently receiving 600-1200 mcg budesonide per day with as-needed beta-agonist Bronchodilator reversibility ≥12% (FEV1) or ≥15% (PEF) FEV1/FVC >50% Symptomatic during final two weeks of the run-in period (800 mcg budesonide per day), as assessed by symptom diary and SABA use (at least one puff per day)
Exclusion criteria	Any other pulmonary disorder Emergency treatment for asthma within a month Hospitalisation within two months Respiratory tract infection within three weeks
Recruitment / selection of participants	No additional information
Intervention(s)	Following a four-week run-in period where all participants received 800 mcg budesonide per day, plus SABA as-needed, those allocated to the intervention received 10 mg montelukast per day in addition to continuing with 800 mcg budesonide per day
Population subgroups	<u>Exacerbations</u> Not reported <u>Atopy</u> Not reported

Comparator	Following a four-week run-in period where all participants received 800 mcg budesonide per day, plus SABA as-needed, those allocated to the comparator doubled their ICS dose to 1600 mcg budesonide per day
Number of participants	75 randomised 37 allocated to ICS+montelukast, 36 completed 38 allocated to ICS, 33 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Per protocol One participant excluded from ICS plus montelukast arm due to taking prednisolone Four protocol violations in the ICS arm - two due to taking prednisolone and two violated inclusion criteria

Study arms

Regular moderate-dose ICS plus montelukast (N = 37)

800 mcg budesonide plus 10 mg montelukast per day

Regular high-dose ICS (N = 38)

1600 mcg budesonide per day

Characteristics

Arm-level characteristics

Characteristic	Regular moderate-dose ICS plus montelukast (N = 37)	Regular high-dose ICS (N = 38)
% Female	n = 23 ; % = 62	n = 18 ; % = 47

Characteristic	Regular moderate-dose ICS plus montelukast (N = 37)	Regular high-dose ICS (N = 38)
Sample size		
Mean age (SD) Mean (SD)	41.5 (11.7)	45 (14.2)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR
PEF L/min Mean (SD)	436.6 (149.3)	449.7 (145)
FEV1 % of predicted Mean (SD)	74.1 (13)	73.6 (14.2)

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous Outcomes

Outcome	Regular moderate-dose ICS plus montelukast, Baseline, N = 37	Regular moderate-dose ICS plus montelukast, 12 week, N = 37	Regular high-dose ICS, Baseline, N = 38	Regular high-dose ICS, 12 week, N = 38
Adverse events Final values No of events	n = NA ; % = NA	n = 28 ; % = 76	n = NA ; % = NA	n = 33 ; % = 87

Adverse events - Polarity - Lower values are better

Continuous Outcomes

Outcome	Regular moderate-dose ICS plus montelukast, Baseline, N = 37	Regular moderate-dose ICS plus montelukast, 12 week, N = 24	Regular high-dose ICS, Baseline, N = 38	Regular high-dose ICS, 12 week, N = 28
Quality of life (Asthma Quality of Life Questionnaire) Scale range: 1-7, final values Mean (SD)	4.96 (1.1)	5.6 (1.03)	4.84 (0.93)	5.36 (0.92)
Lung function (PEF) (L/min) Change scores Mean (95% CI)	NR (NR to NR)	31.7 (10.8 to 52.6)	NR (NR to NR)	32.3 (10.7 to 53.9)

Quality of life (Asthma Quality of Life Questionnaire) - Polarity - Higher values are better

Lung function (PEF) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Continuous Outcomes – Quality of life (Asthma Quality of Life Questionnaire) – Mean (SD) - Regular moderate-dose ICS plus montelukast-Regular high-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and adherence to montelukast and placebo treatments was 77% and 84%, respectively, and paired data reported - excluding results from other participants)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events - No Of Events - Regular moderate-dose ICS plus montelukast-Regular high-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and adherence to montelukast and placebo treatments was 77% and 84%, respectively)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF) – Mean (95% CI) - Regular moderate-dose ICS plus montelukast-Regular high-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and adherence to montelukast and placebo treatments was 77% and 84%, respectively, and paired data reported - excluding results from other participants)*
Overall bias and Directness	Overall Directness	Directly applicable

Bateman, 2004

Bibliographic Reference	Bateman, Eric D; Boushey, Homer A; Bousquet, Jean; Busse, William W; Clark, Tim J H; Pauwels, Romain A; Pedersen, Soren E; Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study.; American journal of respiratory and critical care medicine; 2004; vol. 170 (no. 8); 836-44

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Gaining optimal asthma control (GOAL)
Study type	Randomised controlled trial (RCT)
Study location	No additional information
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by GlaxoSmithKline
Inclusion criteria	Aged 12-80 years At least a 6-month history of asthma

	FEV1 improvement of ≥15% after SABA administration Smoking history of less than 10 pack years No LABA or oral beta agonist use within the previous 2 weeks Not achieving well-controlled asthma during the 4-week run-in
Exclusion criteria	Well controlled asthma on 3 or more weeks of the run-in Change in regular asthma therapy during run-in Emergency department visit due to asthma during run-in Treatment with systemic corticosteroids during run-in Respiratory tract infection during run-in >3 days with morning PEF <50% of predicted Non-compliance with diary record card
Recruitment / selection of participants	Participants were recruited from general practice and hospital clinics
Intervention(s)	During a 4-week run-in period, participants continued to receive their regular ICS treatment. Those who did not achieve at least 2 weeks of well controlled asthma were randomised into the study. Participants received treatment based upon their pre-study ICS treatment; strata 1, no ICS (excluded from this review); strata 2, ≤500 mcg beclomethasone dipropionate equiv.; strata 3, 500-1000 mcg beclomethasone dipropionate equiv. In phase 1, treatment was stepped-up every 12 weeks until totally controlled asthma was achieved or the maximum study dose was achieved (500 mcg fluticasone twice daily or 50/500 salmeterol/fluticasone twice daily). In strata 2, there were three steps of treatment, and in strata 3 only the top two levels applied.

	Treatment steps (all one inhalation, twice daily) Step 1: 100 mcg fluticasone or 50/100 salmeterol/fluticasone Step 2: 250 mcg fluticasone or 50/250 salmeterol/fluticasone Step 3: 500 mcg fluticasone or 50/500 salmeterol/fluticasone Participants remained on the dose at which they achieved asthma control until the end of the study.
Population subgroups	<u>Exacerbations</u> Exacerbation rate between 0.5 and 0.7 in past year <u>Atopy</u> Between 58 and 63% of participants were atopic
Comparator	See intervention
Number of participants	3421 total (1098 (strata 1) excluded from this review due to not receiving ICS at screening) 1161 randomised to salmeterol/fluticasone combination 1157 randomised to fluticasone monotherapy

Duration of follow-up	12 months
Indirectness	Downgraded by one increment due to intervention indirectness - participants could have received low, moderate or high dose ICS or ICS/LABA, depending on the dose at which they achieved asthma control. This review protocol specified moderate-high dose ICS or ICS/LABA treatments only.
Additional comments	Intention to treat

Study arms

Regular low/moderate/high dose ICS/LABA (N = 1161)

50/100, 50/250 or 50/500 mcg salmeterol/fluticasone twice per day

Regular low/moderate/high dose ICS (N = 1157)

100, 250 or 500 mcg fluticasone twice per day

Characteristics

Arm-level characteristics

Characteristic	Regular low/moderate/high dose ICS/LABA (N = 1161)	Regular low/moderate/high dose ICS (N = 1157)
% Female (percent) Nominal	57.5	59.5
Mean age (SD) Mean (SD)	42.2 (16.3)	41.5 (16.2)
Ethnicity Nominal	NR	NR

Characteristic	Regular low/moderate/high dose ICS/LABA (N = 1161)	Regular low/moderate/high dose ICS (N = 1157)
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Average daily reliever inhalations Mean (SD)	1.8 (1.5)	1.8 (1.4)
Lung function (% of predicted) FEV1 Mean (SD)	77 (18)	77 (18)

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	Regular low/moderate/high dose ICS/LABA, Baseline, N = 1133	Regular low/moderate/high dose ICS/LABA, 12 month, N = 1133	Regular low/moderate/high dose ICS, Baseline, N = 1119	Regular low/moderate/high dose ICS, 12 month, N = 1119
Quality of life (Asthma Quality of Life Questionnaire)	NA (NA)	1.24 (1.85)	NA (NA)	1.1 (1.84)

Outcome	Regular low/moderate/high dose ICS/LABA, Baseline, N = 1133	Regular low/moderate/high dose ICS/LABA, 12 month, N = 1133	Regular low/moderate/high dose ICS, Baseline, N = 1119	Regular low/moderate/high dose ICS, 12 month, N = 1119
Change scores, ICS/LABA n= 685, ICS n= 676 Mean (SD)				
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.35 (0.48)	NA (NA)	0.21 (0.47)

Quality of life (Asthma Quality of Life Questionnaire) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Continuous Outcomes – Quality of life (Asthma Quality of Life Questionnaire) – Mean (SD) - Regular moderate dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns arising from low adherence to study medications (89%) and >10% dropout rate with reasons related to intervention efficacy)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1) – Mean (SD) - Regular moderate dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns arising from low adherence to study medications (89%) and >10% dropout rate with reasons related to intervention efficacy)*
Overall bias and Directness	Overall Directness	Directly applicable

Bateman, 2011

Bibliographic Reference	Bateman, Eric D; Kornmann, Oliver; Schmidt, Peter; Pivovarova, Anna; Engel, Michael; Fabbri, Leonardo M; Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma.; The Journal of allergy and clinical immunology; 2011; vol. 128 (no. 2); 315-22

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00350207
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	No additional information
Study dates	July 2006 - April 2008
Sources of funding	Supported by Boehringer Ingelheim and Pfizer
Inclusion criteria	Aged 18-67 years History of asthma with the B16-Arg/Arg genotype

	Receiving 400-1000 mcg budesonide equivalent per day ≥12% and 200 mL increase in FEV1 after receiving SABA Pre-bronchodilator FEV1 <90% of predicted for those on ICS/LABA, <80% for those on ICS monotherapy
Exclusion criteria	Smoking history >10 pack years COPD Serious concomitant illness Concomitant respiratory medication
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 4-week run-in period where all participants continued to receive their usual ICS plus open label 50 mcg salmeterol twice daily, those allocated to the intervention received 2 x 2.5 mcg tiotropium once daily in the evening via a Respimat inhaler in addition to salmeterol-matching placebo twice daily. Salbutamol was provided for use as-needed for rescue medication throughout.
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported

Comparator	Following a 4-week run-in period where all participants continued to receive their usual ICS plus open label 50 mcg salmeterol twice daily, those allocated to the comparator continued to receive 2 x 25 mcg salmeterol twice daily in addition to tiotropium-matching placebo once daily. Salbutamol was provided for use as-needed for rescue medication throughout. *Study also included a placebo arm, not included in this review due to not containing a relevant intervention*
Number of participants	388 randomised 128 allocated to ICS + LAMA, 120 completed 134 allocated to ICS/LABA, 128 completed 126 allocated to placebo (not included in this analysis)
Duration of follow-up	16 weeks (end of treatment), followed by an additional 4-week follow-up (not included in this analysis)
Indirectness	Downgraded by one increment due to population indirectness - 8% of participants had previously received oral xanthines and/or leukotreiene modifiers and one increment due to intervention indirectness - participants added treatment on to current ICS therapy (moderate-high doses, 400-1000 mcg BUD per day), protocol specified low-moderate-dose ICS plus LAMA
Additional comments	ITT

Study arms

Regular low/moderate/high dose ICS plus LAMA (N = 128)
Pre study ICS regimen (400-1000 mcg budesonide per day equivalent) plus 5 mcg tiotropium once daily

Regular low/moderate/high dose ICS/LABA (N = 134)
Pre study ICS regimen (400-1000 mcg budesonide per day equivalent) plus 50 mcg salmeterol twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular low/moderate/high dose ICS plus LAMA (N = 128)	Regular low/moderate/high dose ICS/LABA (N = 134)
% Female Sample size	n = 82 ; % = 64	n = 83 ; % = 62
Mean age (SD) Mean (SD)	43.5 (12.6)	42.3 (13.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 119 ; % = 93	n = 125 ; % = 93
Black Sample size	n = 6 ; % = 5	n = 3 ; % = 2
Asian Sample size	n = 3 ; % = 2	n = 6 ; % = 5
Comorbidities Nominal	NR	NR
ICS dose Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Regular low/moderate/high dose ICS plus LAMA (N = 128)	Regular low/moderate/high dose ICS/LABA (N = 134)
Inhaled glucocorticoids Sample size	n = 128 ; % = 100	n = 133 ; % = 99
LABAs Sample size	n = 95 ; % = 74	n = 93 ; % = 69
Oral xanthines Sample size	n = 4 ; % = 3	n = 4 ; % = 3
leukotriene modifiers Sample size	n = 6 ; % = 5	n = 8 ; % = 6
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	74.1 (16.1)	75.6 (17.6)

Outcomes

Study timepoints

- Baseline
- 16 week

Continuous Outcomes

Outcome	Regular low/moderate/high dose ICS plus LAMA, Baseline, N = 128	Regular low/moderate/high dose ICS plus LAMA, 16 week, N = 128	Regular low/moderate/high dose ICS/LABA, Baseline, N = 134	Regular low/moderate/high dose ICS/LABA, 16 week, N = 134
Quality of life (mini AQLQ) Change scores, scale range 1-7 Mean (SD)	NA (NA)	0.13 (0.77)	NA (NA)	0.28 (0.74)
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-0.07 (2.18)	NA (NA)	-0.27 (2.13)
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.04 (0.34)	NA (NA)	0.06 (0.34)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	0.01 (0.34)	NA (NA)	-0.01 (0.32)

Quality of life (mini AQLQ) - Polarity - Higher values are better
Reliever/rescue medication use - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better
PEF measured over one-week in the evening

Dichotomous Outcomes

Outcome	Regular low/moderate/high dose ICS plus LAMA, Baseline, N = 128	Regular low/moderate/high dose ICS plus LAMA, 16 week, N = 128	Regular low/moderate/high dose ICS/LABA, Baseline, N = 134	Regular low/moderate/high dose ICS/LABA, 16 week, N = 134
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 16 ; % = 12.5	n = NA ; % = NA	n = 17 ; % = 12.7
Hospital admissions Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 4 ; % = 3
Pneumonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 4 ; % = 3	n = NA ; % = NA	n = 2 ; % = 2
Adverse events Final values No of events	n = NA ; % = NA	n = 47 ; % = 37	n = NA ; % = NA	n = 52 ; % = 39

Severe asthma exacerbations - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better
Pneumonia (respiratory tract infections) - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Severe asthma exacerbations defined as those requiring a pharmaceutical product, hospital admissions defined serious adverse events (immediately life-threatening, resulting in significant disability, requiring prolonged hospitalisation, birth defects or linked to a significant hazard)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Continuous Outcomes – Quality of life (miniAQLQ) – Mean (SD) - Regular low-moderate dose ICS plus LAMA-Regular moderate-high dose ICS/LABA-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes - Reliever/rescue medication use – Mean (SD) - Regular low-moderate dose ICS plus LAMA-Regular moderate-high dose ICS/LABA-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1) – Mean (SD) - Regular low-moderate dose ICS plus LAMA-Regular moderate-high dose ICS/LABA-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung function (PEF) - Mean SD - Regular low-moderate dose ICS plus LAMA-Regular moderate-high dose ICS/LABA-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe asthma exacerbations - No Of Events - Regular low-moderate dose ICS plus LAMA-Regular moderate-high dose ICS/LABA-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable

Dichotomous Outcomes – Hospital admissions - No Of Events - Regular low-moderate dose ICS plus LAMA-Regular moderate-high dose ICS/LABA-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Pneumonia (respiratory tract infections) – No Of Events - Regular low-moderate dose ICS plus LAMA-Regular moderate-high dose ICS/LABA-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular low-moderate dose ICS plus LAMA-Regular moderate-high dose ICS/LABA-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Bateman, 2014

Bibliographic Reference	Bateman, Eric D; O'Byrne, Paul M; Busse, William W; Lotvall, Jan; Bleecker, Eugene R; Andersen, Leslie; Jacques, Loretta; Frith, Lucy; Lim, Jessica; Woodcock, Ashley; Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone.; Thorax; 2014; vol. 69 (no. 4); 312-9

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	ClinicalTrials.gov registration number NCT01086384
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	No additional information
Study dates	February 2010 - September 2011
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	Aged ≥12 years NIH defined asthma for ≥1 year

	Using ICS at a dose of ≥200 mcg/day FP equiv. or ICS/LABA at a dose of 200/100-500/100 mcg FP/SAL equiv. for ≥12 weeks, and at ≥4 weeks prior to screening and during run-in ≥1 exacerbation requiring systemic corticosteroids and/or hospital admission in the last year FEV1 50-90% predicted ≥12% and ≥200 mL reversibility with inhaled salbutamol Use of salbutamol and/or asthma symptoms on ≥3 out of 7 consecutive days on their diary card
Exclusion criteria	No additional information
Recruitment / selection of participants	Recruited from 167 centres in 11 countries, method of recruitment not reported
Intervention(s)	Participants randomised to the intervention arm received once daily 100/25 mcg fluticasone furoate/salmeterol administered via a dry powder inhaler. Salbutamol was provided for as-needed relief.
Population subgroups	Exacerbations Exacerbation in past year was an inclusion criteria Atopy Not reported
Comparator	Participants randomised to the comparator arm received once daily 100 mcg fluticasone furoate administered via a dry powder inhaler. Salbutamol was provided for as-needed relief.
Number of participants	2019 randomised 1009 received ICS/LABA

	1010 received ICS monotherapy
Duration of follow-up	24-78 weeks
Indirectness	None
Additional comments	Intention to treat

Study arms

Regular moderate dose ICS/LABA (N = 1009)
100/24 mcg fluticasone furoate/vilanterol once daily

Regular moderate dose ICS (N = 1010)
100 mcg fluticasone furoate once daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 1009)	Regular moderate dose ICS (N = 1010)
% Female Sample size	n = 661 ; % = 66	n = 689 ; % = 68
Mean age (SD) Mean (SD)	41.1 (17.1)	42.3 (16.8)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White	n = 740 ; % = 73	n = 743 ; % = 74

Characteristic	Regular moderate dose ICS/LABA (N = 1009)	Regular moderate dose ICS (N = 1010)
Sample size		
Asian Sample size	n = 112 ; % = 11	n = 110 ; % = 11
African American Sample size	n = 40 ; % = 4	n = 47 ; % = 5
Other Sample size	n = 117 ; % = 12	n = 110 ; % = 11
Comorbidities Nominal	NR	NR
ICS dose Sample size	n = NA ; % = NA	n = NA ; % = NA
ICS Sample size	n = 402 ; % = 40	n = 397 ; % = 39
ICS/LABA Sample size	n = 607 ; % = 60	n = 613 ; % = 61
Asthma control ACQ-7 score Mean (SD)	2.17 (0.75)	2.15 (0.73)

Characteristic	Regular moderate dose ICS/LABA (N = 1009)	Regular moderate dose ICS (N = 1010)
Lung function (% of predicted) FEV1 Mean (SD)	68.8 (10.6)	69 (10.4)

Outcomes

Study timepoints

- Baseline
- 52 week (Treatment was between 24 and 78 weeks, 52 weeks was the average treatment duration.)

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 1009	Regular moderate dose ICS/LABA, 52 week, N = 1009	Regular moderate dose ICS, Baseline, N = 1010	Regular moderate dose ICS, 52 week, N = 1010
Severe asthma exacerbations Number of participants with at least one event No of events	n = NA ; % = NA	n = 154 ; % = 15.3	n = NA ; % = NA	n = 186 ; % = 18.4
Mortality No of events	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 2 ; % = 0
Hospital admissions Final values No of events	n = NA ; % = NA	n = 8 ; % = 0.8	n = NA ; % = NA	n = 9 ; % = 0.9

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 1009	Regular moderate dose ICS/LABA, 52 week, N = 1009	Regular moderate dose ICS, Baseline, N = 1010	Regular moderate dose ICS, 52 week, N = 1010
Adverse events Final values No of events	n = NA ; % = NA	n = 636 ; % = 63	n = NA ; % = NA	n = 652 ; % = 65
Severe exacerbation rate Final values, total number of events Nominal	NA	200	NA	271

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Dichotomous Outcomes – Severe asthma exacerbations - No Of Events - Regular moderate dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns due to no adherence monitoring)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Mortality - No Of Events - Regular moderate dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns due to no adherence monitoring)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Hospital admissions – No Of Events - Regular moderate dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns due to no adherence monitoring)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular moderate dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns due to no adherence monitoring)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Severe exacerbation rate – Nominal - Regular moderate dose ICS/LABA-Regular moderate dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns due to no adherence monitoring)*
Overall bias and Directness	Overall Directness	Directly applicable

Beasley, 2015

Bibliographic Reference	Beasley, Richard W; Donohue, James F; Mehta, Rajendra; Nelson, Harold S; Clay, Michelle; Moton, Allen; Kim, Han-Joo; Hederer, Bettina M; Effect of once-daily indacaterol maleate/mometasone furoate on exacerbation risk in adolescent and adult asthma: a double-blind randomised controlled trial.; BMJ open; 2015; vol. 5 (no. 2); e006131

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00941798
Study type	Randomised controlled trial (RCT)
Study location	New Zealand, USA, India, UK and Switzerland
Study setting	No additional information
Study dates	July 2009 - May 2011
Sources of funding	Sponsored by Novartis Pharma AG
Inclusion criteria	Aged 12–70 years Diagnosis of persistent asthma for ≥6 months

	FEV1 ≥50% of predicted and an increase in FEV1 of ≥12% (and ≥200 mL) after receiving SABA Treated with or qualified for treatment with a LABA/ICS combination Used an ICS for ≥2 months prior to study entry
Exclusion criteria	None specified
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 3-4 week run-in period where all participants received 400 mcg mometasone furoate, one inhalation once per day, those allocated to the intervention received 500/400 mcg indacaterol/mometasone furoate, one inhalation once per day in the evening.
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Following a 3-4 week run-in period where all participants received 400 mcg mometasone furoate, one inhalation once per day, those allocated to the intervention continued to receive 400 mcg mometasone furoate, one inhalation once per day in the evening.
Number of participants	1519 randomised 756 allocated to ICS/LABA, 562 completed, 749 analysed 763 allocated to ICS, 578 completed, 759 analysed
Duration of follow-up	21 months

Indirectness	None
Additional comments	Efficacy analysis using modified intention to treat (excluded those who received no study drug), safety analysis using as treated

Study arms

Regular moderate-dose ICS/LABA (N = 749)
500/400 mcg indacaterol/mometasone furoate, one inhalation once per day

Regular moderate-dose ICS (N = 759)
400 mcg mometasone furoate, one inhalation once per day

Characteristics

Arm-level characteristics

Characteristic	Regular moderate-dose ICS/LABA (N = 749)	Regular moderate-dose ICS (N = 759)
% Female Sample size	n = 436 ; % = 58.2	n = 449 ; % = 59.2
Mean age (SD) Mean (SD)	42.4 (14.8)	42.3 (14.6)
Caucasian Sample size	n = 460 ; % = 61.4	n = 474 ; % = 62.5
Asian Sample size	n = 142 ; % = 19	n = 143 ; % = 18.8
Black	n = 58 ; % = 7.7	n = 53 ; % = 7

Characteristic	Regular moderate-dose ICS/LABA (N = 749)	Regular moderate-dose ICS (N = 759)
Sample size		
Other Sample size	n = 89 ; % = 11.9	n = 89 ; % = 11.7
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Mean ACQ score Nominal	1.7	1.7
Lung function (% of predicted) FEV1 Mean (SD)	75.1 (15.9)	75.5 (15.3)

Outcomes

Study timepoints

- Baseline
- 21 month

Dichotomous Outcomes

Outcome	Regular moderate-dose ICS/LABA, Baseline, N = 749	Regular moderate-dose ICS/LABA, 21 month, N = 749	Regular moderate-dose ICS, Baseline, N = 759	Regular moderate-dose ICS, 21 month, N = 759
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 124 ; % = 16.6	n = NA ; % = NA	n = 171 ; % = 22.5
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0.1
Adverse events Final values No of events	n = NA ; % = NA	n = 554 ; % = 74	n = NA ; % = NA	n = 557 ; % = 73.4
Pneumonia Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 4 ; % = 0.5

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Pneumonia - Polarity - Lower values are better

Continuous Outcomes

Outcome	Regular moderate-dose ICS/LABA, Baseline, N = 749	Regular moderate-dose ICS/LABA, 21 month, N = 675	Regular moderate-dose ICS, Baseline, N = 759	Regular moderate-dose ICS, 21 month, N = 699
Asthma Control (Asthma Control Questionnaire-7) Scale range: 0-6, change scores (follow-up ICS/LABA n=674) Mean (SD)	NA (NA)	-0.55 (0.65)	NA (NA)	-0.32 (0.63)
Lung Function (FEV1) (Litres) Change scores (follow-up ICS n=687) Mean (SD)	NA (NA)	0.06 (1.35)	NA (NA)	-0.07 (1.36)

Asthma Control (Asthma Control Questionnaire-7) - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better

Contrast Outcomes

Outcome	Regular moderate-dose ICS/LABA vs Regular moderate-dose ICS, Baseline, N2 = 759, N1 = 749	Regular moderate-dose ICS/LABA vs Regular moderate-dose ICS, 21 month, N2 = 759, N1 = 749
Severe exacerbation rate Per person year Mean (95% CI)	NA (NA to NA)	0.71 (0.55 to 0.92)

Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Dichotomous Outcomes – Severe asthma exacerbations – No Of Events - Regular moderate-dose ICS/LABA-Regular moderate-dose ICS-t21

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Mortality – No Of Events - Regular moderate-dose ICS/LABA-Regular moderate-dose ICS-t21

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Adverse events – No Of Events - Regular moderate-dose ICS/LABA-Regular moderate-dose ICS-t21

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous Outcomes – Pneumonia – No Of Events - Regular moderate-dose ICS/LABA-Regular moderate-dose ICS-t21

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Asthma Control (Asthma Control Questionnaire-7) – Mean (SD) - Regular moderate-dose ICS/LABA-Regular moderate-dose ICS-t21

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Lung Function (FEV1) – Mean (SD) - Regular moderate-dose ICS/LABA-Regular moderate-dose ICS-t21

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Contrast Outcomes – Severe exacerbation rate – Mean (95% CI) - Regular moderate-dose ICS/LABA-Regular moderate-dose ICS-t21

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Bernstein, 2015

Bibliographic Reference	Bernstein, David I; Bateman, Eric D; Woodcock, Ashley; Toler, William T; Forth, Richard; Jacques, Loretta; Nunn, Carol; O'Byrne, Paul M; Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma.; The Journal of asthma : official journal of the Association for the Care of Asthma; 2015; vol. 52 (no. 10); 1073-83

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01686633
Study type	Randomised controlled trial (RCT)
Study location	Multinational - USA, Russia, Argentina, Ukraine, Romania, Chile, Germany, Poland, Mexico, the Netherlands, Sweden
Study setting	No additional information
Study dates	September 2012 - October 2013
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	>12 years of age Moderate-severe asthma treated with an ICS/LABA for ≥12 weeks

	ICS dose equivalent to >250 mcg fluticasone propionate or 250/50 mcg FP/salmeterol twice daily for ≥4 weeks FEV1 40-80% of predicted FEV1 reversibility ≥12% and ≥200 mL Asthma symptom score ≥3 on the combined day and night asthma symptom scale and/or daily salbutamol use of ≥4 of the last 7 days of the run-in period
Exclusion criteria	History of life-threatening asthma within 5 years Asthma exacerbation requiring oral corticosteroids within 12 weeks, or resulting in hospitalisation within 6 months Concurrent respiratory disease Use of tobacco products within 3 months or historical use of ≥10 pack-years
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 4-week run-in period, where participants maintained their regular ICS dose, but had their LABAs removed, eligible participants randomised to the intervention received either 100/25 or 200/25 mcg fluticasone furoate/vilanterol administered once per day in the evening. Salbutamol was available as-needed throughout the study. Participants were withdrawn if a lack of efficacy was demonstrated, indicated by any of the following: FEV1 measurement <80% of pre-bronchodilator FEV1 at randomization; in the 7 days preceding any visit, ≥4 days in which the peak expiratory flow (PEF) was<80% of the mean morning PEF measured in the week prior to randomization; in the 7 days preceding any visit, ≥3 days in which ≥12 inhalations/day of salbutamol/albuterol were used; severe exacerbation, defined as a deterioration of asthma requiring the use of systemic corticosteroids for ≥3 days, or an in-patient hospitalization/ emergency

	department visit due to asthma that required systemic corticosteroids; or clinical asthma worsening, which in the opinion of the investigator, required additional asthma treatment other than study medication or study-supplied salbutamol/albuterol
Population subgroups	**Exacerbations** Mixed - 29% had an exacerbation in the past year **Atopy** Not reported
Comparator	Following a 4-week run-in period, where participants maintained their regular ICS dose, but had their LABAs removed, eligible participants randomised to the comparator received 100 mcg fluticasone furoate, administered once per day in the evening. Salbutamol was available as-needed throughout the study.
Number of participants	1039 randomised 346 received 100/25 mcg FF/VI, 314 completed 346 received 200/25 mcg FF/VI, 321 completed 347 received 100 mcg FF. 296 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT and per protocol

Study arms

Regular moderate/high dose ICS/LABA (N = 692)
100/25 or 200/25 mcg fluticasone furoate/vilanterol, once daily *Two separate study arms for 100/25 and 200/25 mcg, combined for this review*

Regular moderate dose ICS (N = 347)
100 mcg fluticasone furoate, once daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate/high dose ICS/LABA (N = 692)	Regular moderate dose ICS (N = 347)
% Female Sample size	n = 429 ; % = 62	n = 199 ; % = 57
Mean age (SD) Mean (SD)	46.3 (15.5)	44.7 (15.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 607 ; % = 88	n = 305 ; % = 88
African American/African Heritage Sample size	n = 48 ; % = 7	n = 26 ; % = 7

Characteristic	Regular moderate/high dose ICS/LABA (N = 692)	Regular moderate dose ICS (N = 347)
American Indian or Alaska Native and White Sample size	n = 27 ; % = 4	n = 11 ; % = 3
Japanese/East Asian Heritage/South East Asian Heritage Sample size	n = 4 ; % = 0	n = 4 ; % = 1
Other Sample size	n = 5 ; % = 0	n = 1 ; % = 0
Comorbidities Nominal	NR	NR
ICS dose Sample size	n = NA ; % = NA	n = NA ; % = NA
Moderate-dose ICS Sample size	n = 200 ; % = 29	n = 91 ; % = 26
High-dose ICS Sample size	n = 55 ; % = 8	n = 24 ; % = 7
ICS/LABA combination Sample size	n = 437 ; % = 63	n = 232 ; % = 67
Asthma control	NR	NR

Characteristic	Regular moderate/high dose ICS/LABA (N = 692)	Regular moderate dose ICS (N = 347)
Nominal		
Lung function (% of predicted) FEV1 Mean (SD)	62.4 (10.1)	61.1 (10.3)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate/high dose ICS/LABA , Baseline, N = 692	Regular moderate/high dose ICS/LABA , 12 week, N = 692	Regular moderate dose ICS, Baseline, N = 347	Regular moderate dose ICS, 12 week, N = 347
Quality of life (Asthma Quality of Life Questionnaire) Change scores, scale range: 1-7, ICS/LABA n=643, ICS n=300 Mean (SD)	NA (NA)	0.91 (0.92)	NA (NA)	0.76 (0.92)
Asthma Control (Asthma Control Test) Change scores, scale range: 5-25, ICS/LABA n=644, ICS n=300 Mean (SD)	NA (NA)	5.1 (3.8)	NA (NA)	3.8 (3.8)

Outcome	Regular moderate/high dose ICS/LABA , Baseline, N = 692	Regular moderate/high dose ICS/LABA , 12 week, N = 692	Regular moderate dose ICS, Baseline, N = 347	Regular moderate dose ICS, 12 week, N = 347
Lung function (PEF) (Litres per minute) Change scores, average over 12 weeks, ICS/LABA n=690, ICS n=346 Mean (SD)	NA (NA)	46 (41.9)	NA (NA)	19.1 (41.9)

Quality of life (Asthma Quality of Life Questionnaire) - Polarity - Higher values are better
Asthma Control (Asthma Control Test) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate/high dose ICS/LABA , Baseline, N = 692	Regular moderate/high dose ICS/LABA , 12 week, N = 692	Regular moderate dose ICS, Baseline, N = 347	Regular moderate dose ICS, 12 week, N = 347
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 7 ; % = 1	n = NA ; % = NA	n = 7 ; % = 2
Pneumonia Final values No of events	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 2 ; % = 1
Adverse events Final values No of events	n = NA ; % = NA	n = 250 ; % = 36	n = NA ; % = NA	n = 127 ; % = 37

Severe asthma exacerbations - Polarity - Lower values are better

Pneumonia - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Continuous Outcomes – Quality of life (Asthma Quality of Life Questionnaire) – Mean (SD) - Regular moderate-high dose ICS/LABA -Regular moderate-high dose ICS inhaler-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes – Asthma Control (Asthma Control Test) – Mean (SD) - Regular moderate-high dose ICS/LABA - Regular moderate-high dose ICS inhaler-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes - Lung function (PEF) – Mean (SD) - Regular moderate-high dose ICS/LABA -Regular moderate-high dose ICS inhaler-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA -Regular moderate-high dose ICS inhaler-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia-NoOfEvents-Regular moderate-high dose ICS/LABA -Regular moderate-high dose ICS inhaler-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA -Regular moderate-high dose ICS inhaler-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Bleecker, 2014

Bibliographic Reference	Bleecker, Eugene R; Lotvall, Jan; O'Byrne, Paul M; Woodcock, Ashley; Busse, William W; Kerwin, Edward M; Forth, Richard; Medley, Hilary V; Nunn, Carol; Jacques, Loretta; Bateman, Eric D; Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial.; The journal of allergy and clinical immunology. In practice; 2014; vol. 2 (no. 5); 553-61

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01165138
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	64 centres in 6 countries
Study dates	August 2010 - October 2011
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	≥12 years of age ≥12% and ≥200 mL reversibility after SABA

	FEV1 40-90% of predicted Receiving a stable low-moderate dose of ICS (100-250 mcg FP twice daily) or a low-dose of ICS/LABA (100/50 mcg FP/SAL twice daily) for ≥4 weeks prior to screening
Exclusion criteria	None reported
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 4-week run-in period where participants received ICS monotherapy, those allocated to the intervention arm received 100/25 mcg fluticasone furoate/vilanterol once daily in the evening (corresponds to 92/22 mcg emitted dose) via a dry powder inhaler
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Following a 4-week run-in period where participants received ICS monotherapy, those allocated to the comparator arm received 100 mcg fluticasone furoate once daily in the evening via a dry powder inhaler *Study also included a placebo arm, not included in this review due to not containing a relevant intervention*

Number of participants	609 randomised, 515 completed 205 received ICS monotherapy 201 received ICS/LABA 203 received placebo (not included in this review)
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular moderate dose ICS/LABA (N = 201)
100/25 mcg fluticasone furoate/vilanterol combination inhaler once daily

Regular moderate dose ICS (N = 205)
100 mcg fluticasone furoate once daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 201)	Regular moderate dose ICS (N = 205)
% Female Sample size	n = 116 ; % = 58	n = 126 ; % = 61
Mean age (SD)	40.7 (16.4)	40.4 (16.8)

Characteristic	Regular moderate dose ICS/LABA (N = 201)	Regular moderate dose ICS (N = 205)
Mean (SD)		
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 172 ; % = 86	n = 171 ; % = 83
Asian Sample size	n = 16 ; % = 8	n = 16 ; % = 8
Other Sample size	n = 13 ; % = 6	n = 18 ; % = 8
Comorbidities Nominal	NR	NR
ICS dose Sample size	n = NA ; % = NA	n = NA ; % = NA
ICS monotherapy Sample size	n = 120 ; % = 60	n = 122 ; % = 60
ICS/Salmeterol Sample size	n = 54 ; % = 27	n = 57 ; % = 28
ICS/Formoterol Sample size	n = 27 ; % = 13	n = 26 ; % = 13

Characteristic	Regular moderate dose ICS/LABA (N = 201)	Regular moderate dose ICS (N = 205)
Asthma control (%) Rescue-free 24-hour periods Mean (SD)	13.4 (27.8)	15.3 (29.2)
Lung function (% of predicted) FEV1 Mean (SD)	70.62 (11.88)	70.49 (11.01)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 201	Regular moderate dose ICS/LABA, 12 week, N = 179	Regular moderate dose ICS, Baseline, N = 205	Regular moderate dose ICS, 12 week, N = 185
Quality of Life (AQLQ+12) Change scores, scale range: 1-7 Mean (SD)	NA (NA)	0.91 (0.74)	NA (NA)	0.76 (0.75)
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.37 (0.43)	NA (NA)	0.33 (0.43)

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 201	Regular moderate dose ICS/LABA, 12 week, N = 179	Regular moderate dose ICS, Baseline, N = 205	Regular moderate dose ICS, 12 week, N = 185
Asthma control (ACT) Change scores, scale range 5-25 Mean (SD)	NA (NA)	4.4 (3.1)	NA (NA)	3.8 (3.2)
Reliever Medication Use (rescue-free 24-hour periods) (%) Change scores Mean (SD)	NA (NA)	38.7 (32.5)	NA (NA)	28.1 (32.5)

Quality of Life (AQLQ+12) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better
Asthma control (ACT) - Polarity - Higher values are better
Reliever Medication Use (rescue-free 24-hour periods) - Polarity - Higher values are better
Quality of life: ICS/LABA n=180, ICS n=184; Lung function: ICS/LABA n=201, ICS n=203; Asthma Control: ICS/LABA n=185, ICS n=189; Reliever/Rescue Medication Use: ICS/LABA n=183, ICS n=180

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 201	Regular moderate dose ICS/LABA, 12 week, N = 201	Regular moderate dose ICS, Baseline, N = 205	Regular moderate dose ICS, 12 week, N = 205
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 4 ; % = 2

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 201	Regular moderate dose ICS/LABA, 12 week, N = 201	Regular moderate dose ICS, Baseline, N = 205	Regular moderate dose ICS, 12 week, N = 205
Pneumonia Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Severe asthma exacerbations - Polarity - Lower values are better
Pneumonia - Polarity - Lower values are better
Mortality - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-QualityofLife(AQLQ+12)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and >10% dropout rate with no information on rates per group or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and >10% dropout rate with no information on rates per group or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Asthmacontrol(ACT)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and >10% dropout rate with no information on rates per group or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-RelieverMedicationUse(rescue-free24-hourperiods)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and >10% dropout rate with no information on rates per group or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and >10% dropout rate with no information on rates per group or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and >10% dropout rate with no information on rates per group or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and >10% dropout rate with no information on rates per group or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

Bousquet, 2007

Bibliographic Reference	Bousquet, Jean; Boulet, Louis-Philippe; Peters, Matthew J; Magnussen, Helgo; Quiralte, Joaquin; Martinez-Aguilar, Nora E; Carlsheimer, Asa; Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone.; Respiratory medicine; 2007; vol. 101 (no. 12); 2437-46

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Study code D589 0C00002
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	No additional information
Study dates	May 2005 - May 2006
Sources of funding	Funded by AstraZeneca
Inclusion criteria	≥12 years of age Persistent asthma, treated with ICS alone (800-1600 mcg/day) or ICS/LABA combination (400-1000 mcg/day) for ≥3 months prior to study entry

	FEV1 ≥50% predicted ≥12% reversibility after SABA ≥1 clinically important exacerbation in the past year Used SABA on ≥5 of 7 days of the run-in, but no more than 8 inhalations in a single day
Exclusion criteria	Recent respiratory tract infection Use of systemic corticosteroids within 30 days of study entry Use of any beta blocking agent Smoking history ≥10 pack years
Recruitment / selection of participants	Recruited from 184 centres, method not reported
Intervention(s)	After a 2-week run-in on regular maintenance ICS (plus LABA if used pre-enrolment) plus terbutaline as needed, participants were randomised. Those randomised to the intervention received 160/4.5 mcg budesonide/formoterol, two inhalations, twice daily plus as needed for symptom relief.
Population subgroups	<u>Exacerbations</u> Exacerbation in past year was part of the inclusion criteria <u>Atopy</u> Not reported

Comparator	After a 2-week run-in on regular maintenance ICS (plus LABA if used pre-enrolment) plus terbutaline as needed, participants were randomised. Those randomised to the comparator received 50/500 mcg salmeterol/fluticasone, one inhalation, twice daily plus 0.4 mg terbutaline as needed for symptom relief.
Number of participants	2309 randomised 1151 received regular ICS/LABA + as needed ICS/LABA 1153 received regular ICS/LABA + as needed SABA
Duration of follow-up	6 months
Indirectness	None
Additional comments	Intention to treat

Study arms

Moderate dose ICS/formoterol MART (N = 1154)

160/4.5 mcg budesonide/formoterol two inhalations, twice daily plus as needed for symptom relief

Regular high dose ICS/LABA (N = 1155)

50/500 mcg salmeterol/fluticasone one inhalation, twice daily plus 0.4 mg terbutaline as needed for symptom relief

Characteristics

Arm-level characteristics

Characteristic	Moderate dose ICS/formoterol MART (N = 1154)	Regular high dose ICS/LABA (N = 1155)
% Female Sample size	n = 711 ; % = 62	n = 711 ; % = 62

Characteristic	Moderate dose ICS/formoterol MART (N = 1154)	Regular high dose ICS/LABA (N = 1155)
Mean age (SD) Nominal	40	39
Mean age (SD) Range	12 to 80	12 to 80
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Nominal	705	720
ICS dose Range	250 to 1600	200 to 2000
Asthma control Average number of exacerbations in past year Nominal	1.8	1.9
Asthma control Average number of exacerbations in past year Range	1 to 10	1 to 24

Characteristic	Moderate dose ICS/formoterol MART (N = 1154)	Regular high dose ICS/LABA (N = 1155)
Lung function (% of predicted) FEV1 Nominal	70.2	71
Lung function (% of predicted) FEV1 Range	45 to 114	45 to 222

Outcomes

Study timepoints

- Baseline
- 6 month

Dichotomous Outcomes

Outcome	Moderate dose ICS/formoterol MART, Baseline, N = 1154	Moderate dose ICS/formoterol MART, 6 month, N = 1151	Regular high dose ICS/LABA, Baseline, N = 1155	Regular high dose ICS/LABA, 6 month, N = 1153
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 108 ; % = 9.4	n = NA ; % = NA	n = 130 ; % = 11.3
Hospital admissions Final values No of events	n = NA ; % = NA	n = 39 ; % = 3.4	n = NA ; % = NA	n = 59 ; % = 5.1

Outcome	Moderate dose ICS/formoterol MART, Baseline, N = 1154	Moderate dose ICS/formoterol MART, 6 month, N = 1151	Regular high dose ICS/LABA, Baseline, N = 1155	Regular high dose ICS/LABA, 6 month, N = 1153
Mortality Final values No of events	n = NA ; % = NA	n = 1 ; % = 0.1	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 450 ; % = 39	n = NA ; % = NA	n = 462 ; % = 40
Severe exacerbation rate Final values, total number of events Nominal	NA	137	NA	173

Severe asthma exacerbations - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Severe exacerbation rate - Polarity - Lower values are better

Contrast Outcomes

Outcome	Moderate dose ICS/formoterol MART vs Regular high dose ICS/LABA, Baseline, N2 = NA, N1 = NA	Moderate dose ICS/formoterol MART vs Regular high dose ICS/LABA, 6 month, N2 = 1155, N1 = 1154
Asthma control (ACQ-5) Scale range: 0-6, final values Mean (95% CI)	NA (NA to NA)	-0.02 (-0.07 to 0.04)

Outcome	Moderate dose ICS/formoterol MART vs Regular high dose ICS/LABA, Baseline, N2 = NA, N1 = NA	Moderate dose ICS/formoterol MART vs Regular high dose ICS/LABA, 6 month, N2 = 1155, N1 = 1154
Lung function (PEF) (Litres per minute) Change scores Mean (95% CI)	NA (NA to NA)	-0.8 (-4.4 to 2.8)
Reliever/rescue medication use (Puffs per day) Final values Mean (95% CI)	NA (NA to NA)	-0.04 (-0.12 to 0.04)

Asthma control (ACQ-5) - Polarity - Lower values are better
Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular ICS/LABA + ICS/LABA as needed-Regular moderate-high dose ICS/LABA-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Hospitaladmissions-NoOfEvents-Regular ICS/LABA + ICS/LABA as needed-Regular moderate-high dose ICS/LABA-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular ICS/LABA + ICS/LABA as needed-Regular moderate-high dose ICS/LABA-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular ICS/LABA + ICS/LABA as needed-Regular moderate-high dose ICS/LABA-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Asthmacontrol(ACQ-5)-MeanNineFivePercentCI-Regular ICS/LABA + ICS/LABA as needed-Regular moderate-high dose ICS/LABA-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Lungfunction(PEF)-MeanNineFivePercentCI-Regular ICS/LABA + ICS/LABA as needed-Regular moderate-high dose ICS/LABA-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Reliever/rescuemedicationuse-MeanNineFivePercentCI-Regular ICS/LABA + ICS/LABA as needed-Regular moderate-high dose ICS/LABA-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeexacerbationrate-Nominal-Moderate dose ICS/formoterol MART-Regular high dose ICS/LABA-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Busse, 2013

Bibliographic Reference	Busse, William W; O'Byrne, Paul M; Bleecker, Eugene R; Lotvall, Jan; Woodcock, Ashley; Andersen, Leslie; Hicks, Wesley; Crawford, Jodie; Jacques, Loretta; Apoux, Ludovic; Bateman, Eric D; Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the beta2 agonist vilanterol administered once daily for 52 weeks in patients >=12 years old with asthma: a randomised trial.; Thorax; 2013; vol. 68 (no. 6); 513-20

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01018186
Study type	Randomised controlled trial (RCT)
Study location	Multinational - USA, Germany, Ukraine and Thailand
Study setting	No additional information
Study dates	October 2009 - May 2011
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	≥12 years of age Diagnosed with asthma as per NIH criteria

	Receiving ICS at a dose of 500-1000 mcg per day with or without additional controller therapy for at least 4 weeks FEV1 ≥50% of predicted ≥12% and 200 mL FEV1 reversibility after receiving SABA
Exclusion criteria	Exacerbation requiring oral corticosteroids within 3 months History of life threatening asthma Concurrent respiratory disease Current smoker, or smoking history >10 pack years
Recruitment / selection of participants	Recruited from 45 centres. method not reported
Intervention(s)	Following a 2-week run-in period, those allocated to the intervention arms received either 100/25 (emitted dose of 92/22) or 200/25 (emitted dose of 184/22) mcg fluticasone furoate/vilanterol once daily in the evening via a dry powder inhaler. Participants also received a placebo DISKUS/ACCUHALER to maintain blinding. *Two study arms containing 100/25 and 200/25 mcg fluticasone furoate/vilanterol combined for this review*
Population subgroups	**Exacerbations** 70% no exacerbation, 20% 1 exacerbation, 10% 2 exacerbations in past 12 months

	Atopy Not reported
Comparator	Following a 2-week run-in period, those allocated to the comparator arm received 500 mcg fluticasone propionate twice daily in the via a DISKUS/ACCUHALER. Participants also received a placebo dry powder inhaler to maintain blinding.
Number of participants	503 randomised 403 allocated to ICS/LABA, 322 completed 100 allocated to ICS, 71 completed
Duration of follow-up	52 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular moderate/high dose ICS/LABA (N = 403)
100/25 or 200/25 mcg fluticasone furoate/vilanterol once daily in the evening *two study arms containing different doses combined for this review*

Regular high dose ICS (N = 100)
500 mcg fluticasone propionate twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate/high dose ICS/LABA (N = 403)	Regular high dose ICS (N = 100)
% Female Sample size	n = 254 ; % = 63	n = 62 ; % = 62
Mean age (SD) Mean (SD)	39.1 (15.8)	38.6 (16)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 269 ; % = 67	n = 68 ; % = 68
Asian Sample size	n = 101 ; % = 25	n = 26 ; % = 26
African American/African Heritage Sample size	n = 32 ; % = 8	n = 6 ; % = 6
Other Sample size	n = 1 ; % = 0	n = 0 ; % = 0
Comorbidities Nominal	NR	NR
ICS dose	NR	NR

Characteristic	Regular moderate/high dose ICS/LABA (N = 403)	Regular high dose ICS (N = 100)
Nominal		
Asthma control Nominal	NR	NR
Lung function (Litres) FEV1 Mean (SD)	74.2 (13.8)	75.2 (12.5)

Outcomes

Study timepoints

- Baseline
- 52 week

Dichotomous Outcomes

Outcome	Regular moderate/high dose ICS/LABA, Baseline, N = 403	Regular moderate/high dose ICS/LABA, 52 week, N = 403	Regular high dose ICS, Baseline, N = 100	Regular high dose ICS, 52 week, N = 100
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 9 ; % = 2	n = NA ; % = NA	n = 3 ; % = 3
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Regular moderate/high dose ICS/LABA, Baseline, N = 403	Regular moderate/high dose ICS/LABA, 52 week, N = 403	Regular high dose ICS, Baseline, N = 100	Regular high dose ICS, 52 week, N = 100
Hospital admissions Final values No of events	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 2 ; % = 2
Pneumonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 11 ; % = 3	n = NA ; % = NA	n = 7 ; % = 7
Adverse events Final values No of events	n = NA ; % = NA	n = 262 ; % = 65	n = NA ; % = NA	n = 66 ; % = 66

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better
Pneumonia (respiratory tract infections) - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(22% dropout rate with 10% difference between study arms and reasons related to participant's health)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(22% dropout rate with 10% difference between study arms and reasons related to participant's health)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Hospitaladmissions-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(22% dropout rate with 10% difference between study arms and reasons related to participant's health)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia(respiratorytractinfections)-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(22% dropout rate with 10% difference between study arms and reasons related to participant's health)*
Overall bias and Directness	Overall Directness	Indirectly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(22% dropout rate with 10% difference between study arms and reasons related to participant's health)*
Overall bias and Directness	Overall Directness	Directly applicable

Corren, 2013

Bibliographic Reference	Corren, Jonathan; Mansfield, Lyndon E; Pertseva, Tetyana; Blahzko, Viktor; Kaiser, Kirsten; Efficacy and safety of fluticasone/formoterol combination therapy in patients with moderate-to-severe asthma.; Respiratory medicine; 2013; vol. 107 (no. 2); 180-95

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	EudraCT number: 2006-005989-39; US NCT number: NCT00393952
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	No additional information
Study dates	July 2006 - April 2008
Sources of funding	Sponsored by SkyePharma
Inclusion criteria	≥12 years of age Asthma diagnosis for ≥12 months

	ICS therapy for ≥4 weeks prior to screening at a dose ≤500 mcg per day fluticasone equiv. FEV1 between 40-80% predicted FEV1 reversibility within 12 months of screening, defined as >14.5% increase after SABA ≥2 SABA inhalations on ≥3 out of 7 consecutive days of the 2-week run-in as well as symptoms on ≥3 days or 1 night
Exclusion criteria	History of life threatening asthma Hospitalisation or intubation for asthma in the previous 12 months Systemic corticosteroid use in the past 3 months Omalizumab use in the past 6 months Leukotriene receptor agonist use in the past week COPD, cystic fibrosis or bronchiectasis Respiratory tract infection within 4 weeks Significant medical illness Smoking history ≥10 pack years Hypersensitivity to study medication

	Receiving beta-blockers, tricyclic antidepressants, monoamine oxidase inhibitors, quinidine-type antiarrhythmics or drugs known to inhibit CYP3A4 within the week prior to screening
Recruitment / selection of participants	Recruited from 78 centres in North America and Europe, method not reported
Intervention(s)	Following a ~2 week run-in period where participants received 100 or 200 mcg fluticasone, those randomised to the intervention arm received 125/5 mcg fluticasone/formoterol, two inhalations twice daily, plus twice daily placebo, plus salbutamol for symptom relief.
Population subgroups	Exacerbations Not reported Atopy Not reported
Comparator	Following a ~2 week run-in period where participants received 100 or 200 mcg fluticasone, those randomised to the comparator arm received 125 mcg fluticasone, two inhalations twice daily, plus twice daily placebo plus salbutamol for symptom relief. This study also contained an additional three arms where participants received; placebo alone, formoterol alone or 50/50mcg fluticasone/formoterol two inhalations twice daily. These were excluded from this analysis due to not being relevant comparators, or using doses that did not match those specified in the protocol.
Number of participants	557 randomised 110 received regular ICS/LABA 113 received regular ICS

Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat with last observation carried forward

Study arms

Regular moderate dose ICS/LABA (N = 110)

125/5 mcg fluticasone/formoterol, two inhalations twice daily plus placebo

Regular moderate dose ICS (N = 113)

125 mcg fluticasone, two inhalations twice daily plus placebo

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 110)	Regular moderate dose ICS (N = 113)
% Female Sample size	n = 64 ; % = 58.2	n = 63 ; % = 55.8
Mean age (SD) Mean (SD)	44.8 (15.7)	41.9 (15.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 92 ; % = 83.6	n = 89 ; % = 78.8

Characteristic	Regular moderate dose ICS/LABA (N = 110)	Regular moderate dose ICS (N = 113)
Black Sample size	n = 13 ; % = 11.8	n = 12 ; % = 10.6
Hispanic Sample size	n = 5 ; % = 4.5	n = 10 ; % = 8.8
Other Sample size	n = 0 ; % = 0	n = 2 ; % = 1.8
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control (% of predicted) FEV1 Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	64.9 (10.5)	65.7 (18.4)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 108	Regular moderate dose ICS/LABA, 12 week, N = 108	Regular moderate dose ICS, Baseline, N = 109	Regular moderate dose ICS, 12 week, N = 109
Reliever/rescue medication use (Inhalations per day) Change scores, ICS/LABA n=103, ICS n=106 Mean (SD)	NA (NA)	-1.89 (2.2)	NA (NA)	-1.22 (2.31)
Lung Function (FEV1) (% predicted) Change scores Mean (SD)	NA (NA)	0.18 (0.45)	NA (NA)	0.11 (0.43)
Lung function (PEF) (litres/minute) Change scores, ICS/LABA n=103, ICS n=104 Mean (SD)	NA (NA)	28.37 (53.34)	NA (NA)	12.47 (51.52)

Reliever/rescue medication use - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 108	Regular moderate dose ICS/LABA, 12 week, N = 108	Regular moderate dose ICS, Baseline, N = 109	Regular moderate dose ICS, 12 week, N = 109
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 4 ; % = 3.7	n = NA ; % = NA	n = 5 ; % = 4.6
Mortality No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 34 ; % = 31	n = NA ; % = NA	n = 48 ; % = 43

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Reliever/rescuemedicationuse-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(86.7% adherence to study medication and 23% dropout rate with reasons related to participant's health status)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(86.7% adherence to study medication and 23% dropout rate with reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(morningPEF)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(86.7% adherence to study medication and 23% dropout rate with reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(86.7% adherence to study medication and 23% dropout rate with reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(86.7% adherence to study medication and 23% dropout rate with reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(86.7% adherence to study medication and 23% dropout rate with reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Emami, 2014

Bibliographic Reference	Emami, Mohammad; Tayebi, Azadeh; Gharipour, Mojgan; Farzamnia, Somayeh; Temyarti, Akbar Kargari; Comparing clinical efficacy of Symbicort versus Pulmicort in reducing asthma symptom and improving its control.; Advanced biomedical research; 2014; vol. 3; 86

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	No additional information
Study dates	2012-2013
Sources of funding	No additional information
Inclusion criteria	18- 65 years of age Moderate asthma (symptoms begin with light exercise, 1-2 asthma attacks per week, and FEV1 60%-80%) or severe asthma (severe limitations in performing activities, >2 asthma attacks per week, and FEV1 <60%)

Exclusion criteria	Inability to perform spirometry testing Underlying disease aggravating asthma Current smoking Respiratory infection within 30 days Using a rectal or oral or parenteral glucocorticoid within 30 days Previous treatment with budesonide/formoterol for both maintenance and reliever therapy Instability at study entry Pregnancy
Recruitment / selection of participants	Recruited from a single hospital, method not reported
Intervention(s)	Participants allocated to the intervention arm received 160/4.5 mcg budesonide/formoterol (Symbicort), two inhalations twice per day *Study also included an arm where participants received 80/4.5 mcg budesonide/formoterol, two inhalations twice daily, excluded from this review due to not being a moderate-high dose ICS/LABA*
Population subgroups	**Exacerbations** Not reported

	Atopy Not reported
Comparator	Participants allocated to the comparator arm received 180 mcg budesonide (Pulmicort), two inhalations twice per day
Number of participants	76 randomised 24 received moderate-high dose ICS/LABA 27 received ICS 25 received low-dose ICS/LABA (excluded from this review)
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Unclear

Study arms

Regular moderate dose ICS/LABA (N = 24)
160/4.5 mcg budesonide/formoterol, two inhalations twice daily

Regular moderate dose ICS (N = 27)
180 mcg budesonide, two inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 24)	Regular moderate dose ICS (N = 27)
% Female Sample size	n = 12 ; % = 50	n = 12 ; % = 44
Mean age (SD) Mean (SD)	46 (12.36)	40.26 (10.61)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control ACT Mean (SD)	13.75 (2.54)	13.22 (2.22)
Lung function (% of predicted) FEV1 Mean (SD)	57.04 (8.19)	56.96 (8.51)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 24	Regular moderate dose ICS/LABA, 12 week, N = 24	Regular moderate dose ICS, Baseline, N = 27	Regular moderate dose ICS, 12 week, N = 27
Asthma Control (Asthma Control Test) Final values, scale range: 5-25 Mean (SD)	13.75 (2.54)	20.17 (2.04)	13.22 (2.22)	18.59 (1.89)
Lung Function (FEV1) (% of predicted) Final values Mean (SD)	57.04 (8.19)	75.67 (8.68)	56.96 (8.51)	68.07 (8.19)

Asthma Control (Asthma Control Test) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-AsthmaControl(AsthmaControlTest)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence data reported and lack of detail in description of statistical methods applied)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence data reported and lack of detail in description of statistical methods applied)*
Overall bias and Directness	Overall Directness	Directly applicable

Fish, 2001

Bibliographic Reference	Fish, J E; Israel, E; Murray, J J; Emmett, A; Boone, R; Yancey, S W; Rickard, K A; Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy.; Chest; 2001; vol. 120 (no. 2); 423-30

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA and Puerto Rico
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by Glaxo Wellcome
Inclusion criteria	≥15 years of age Diagnosed with asthma for ≥6 months

	Symptomatic despite receiving ICS for ≥6 weeks and at a constant dose for ≥30 days FEV1 50-80% of predicted at screening and after the run-in ≥12% increase in FEV1 after receiving SABA one or more of: average ≥4 SABA uses per day, symptom score ≥2 on ≥3 days and awakening due to asthma on ≥3 days on the 7 days prior to randomisation
Exclusion criteria	Pregnant or lactating
Recruitment / selection of participants	Recruited from 71 centres, method not reported
Intervention(s)	Participants allocated to the LABA arm received 50 mcg salmeterol, taken twice daily, in addition to continuing their regular ICS therapy at the same dose. Participants were also provided with albuterol inhalers for use as-needed for symptom relief
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Participants allocated to the montelukast arm received 10 mg montelukast, taken once daily, in addition to continuing their regular ICS therapy at the same dose. Participants were also provided with albuterol inhalers for use as-needed for symptom relief
Number of participants	948 randomised 476 received ICS/LABA 472 received ICS + montelukast

Duration of follow-up	12 weeks
Indirectness	Downgraded by one increment due to intervention indirectness - participants were kept on their usual ICS regimen, which could have been low, moderate or high dose, in addition to study drugs
Additional comments	Mixed, intention to treat for safety outcomes and available case analysis for efficacy outcomes

Study arms

Regular low/moderate/high dose ICS/LABA (N = 476)
Pre-study ICS plus 50 mcg salmeterol twice per day

Regular low/moderate/high dose ICS plus montelukast (N = 472)
Pre-study ICS plus 10 mg montelukast once per day

Characteristics

Arm-level characteristics

Characteristic	Regular low/moderate/high dose ICS/LABA (N = 476)	Regular low/moderate/high dose ICS plus montelukast (N = 472)
% Female Sample size	n = 288 ; % = 61	n = 292 ; % = 62
Mean age (SD) Mean (SD)	39.9 (13.1)	39.5 (13)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Regular low/moderate/high dose ICS/LABA (N = 476)	Regular low/moderate/high dose ICS plus montelukast (N = 472)
White Sample size	n = 413 ; % = 87	n = 393 ; % = 83
Black Sample size	n = 29 ; % = 6	n = 42 ; % = 9
Asian Sample size	n = 5 ; % = 1	n = 9 ; % = 2
American Hispanic Sample size	n = 25 ; % = 5	n = 28 ; % = 6
Other Sample size	n = 4 ; % = 1	n = 0 ; % = 0
Comorbidities Nominal	NR	NR
ICS dose Nominal	NA	NA
ICS dose Range	NA to NA	NA to NA
Fluticasone Nominal	468	497

Characteristic	Regular low/moderate/high dose ICS/LABA (N = 476)	Regular low/moderate/high dose ICS plus montelukast (N = 472)
Fluticasone Range	44 to 1320	176 to 1760
Triamcinolone Nominal	548	557
Triamcinolone Range	200 to 1600	100 to 1600
Beclomethasone Nominal	269	261
Beclomethasone Range	84 to 672	84 to 672
Budesonide Nominal	714	588
Budesonide Range	400 to 1200	84 to 800
Flunisolide Nominal	1117	1036
Flunisolide Range	250 to 2000	800 to 1500

Characteristic	Regular low/moderate/high dose ICS/LABA (N = 476)	Regular low/moderate/high dose ICS plus montelukast (N = 472)
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	68.1 (8.7)	68.6 (8.7)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular low/moderate/high dose ICS/LABA, Baseline, N = 476	Regular low/moderate/high dose ICS/LABA, 12 week, N = 452	Regular low/moderate/high dose ICS plus montelukast, Baseline, N = 472	Regular low/moderate/high dose ICS plus montelukast, 12 week, N = 448
Reliever medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-1.9 (2.13)	NA (NA)	-1.66 (2.33)
Severe exacerbation rate Final values, total	NA	27	NA	24

Outcome	Regular low/moderate/high dose ICS/LABA, Baseline, N = 476	Regular low/moderate/high dose ICS/LABA, 12 week, N = 452	Regular low/moderate/high dose ICS plus montelukast, Baseline, N = 472	Regular low/moderate/high dose ICS plus montelukast, 12 week, N = 448
number of exacerbations Nominal				

Reliever medication use - Polarity - Lower values are better
Severe exacerbation rate - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Regular low/moderate/high dose ICS/LABA, Baseline, N = 476	Regular low/moderate/high dose ICS/LABA, 12 week, N = 476	Regular low/moderate/high dose ICS plus montelukast, Baseline, N = 472	Regular low/moderate/high dose ICS plus montelukast, 12 week, N = 472
Severe asthma exacerbations Final values, defined as worsening of symptoms requiring treatment beyond study drugs or SABA No of events	n = NA ; % = NA	n = 26 ; % = 6	n = NA ; % = NA	n = 23 ; % = 5
Pneumonia Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0

Severe asthma exacerbations - Polarity - Lower values are better
Pneumonia - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular low-moderate dose ICS plus montelukast-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on randomisation method, switching rate between study arms, adherence to study medication, or details on statistical methods used to analyse data)*
Overall bias and Directness	Overall Directness	Indirectly applicable

DichotomousOutcomes-Pneumonia-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular low-moderate dose ICS plus montelukast-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on randomisation method, switching rate between study arms, adherence to study medication, or details on statistical methods used to analyse data)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Relievermedicationuse-MeanSD-Regular moderate-high dose ICS/LABA-Regular low-moderate dose ICS plus montelukast-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on randomisation method, switching rate between study arms, adherence to study medication, or details on statistical methods used to analyse data)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Severeexacerbationrate-Nominal-Regular low/moderate/high dose ICS/LABA-Regular low/moderate/high dose ICS plus montelukast-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on randomisation method, switching rate between study arms, adherence to study medication, or details on statistical methods used to analyse data)*
Overall bias and Directness	Overall Directness	Indirectly applicable

Hoshino, 2019

Bibliographic Reference	Hoshino, Makoto; Akitsu, Kenta; Ohtawa, Junichi; Comparison between montelukast and tiotropium as add-on therapy to inhaled corticosteroids plus a long-acting beta2-agonist in for patients with asthma.; The Journal of asthma : official journal of the Association for the Care of Asthma; 2019; vol. 56 (no. 9); 995-1003

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Registered with the University Hospital Medical Information Network (http://www.umin.ac.jp. UMIN000019042)
Study type	Randomised controlled trial (RCT)
Study location	No additional information
Study setting	No additional information
Study dates	No additional information
Sources of funding	None reported
Inclusion criteria	Asthma for ≥3 months Symptomatic at screening

	Reversible airway obstruction (>12% increase in FEV1 after receiving SABA) Receiving ICS plus LABA for ≥4 weeks prior to screening FEV1 >60% predicted Non-smokers or ex-smokers with less than 5-pack years who had stopped at least a year prior to screening
Exclusion criteria	Diagnosis of COPD or any other respiratory disease Glaucoma, prostatic hyperplasia or respiratory tract infection within 2 weeks prior to screening
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 4-week run-in period where participants received 160/4.5 budesonide/formoterol combination inhaler, two inhalations once daily, those randomised to the montelukast arm received 10 mg oral montelukast once daily in addition to their daily ICS/LABA therapy. Those randomised to the LAMA arm received 5 mcg tiotropium in addition to their daily ICS/LABA therapy. All participants were given a SABA inhaler for symptom relief.
Population subgroups	<u>Exacerbations</u> Majority not exacerbating in the past year; montelukast 34%, LAMA 36%, placebo 37% <u>Atopy</u> Majority atopic; Montelukast n=18/28, LAMA n=20/29, placebo n=21/30
Comparator	See intervention
Number of participants	102 randomised, 87 completed

	28 received ICS/LABA + montelukast 29 received ICS/LABA + LAMA 30 received ICS/LABA + placebo
Duration of follow-up	48 weeks
Indirectness	None
Additional comments	Per protocol

Study arms

Regular low dose ICS/LABA + montelukast (N = 28)

160/4.5 mcg budesonide/formoterol combination inhaler, two inhalations once daily plus 10 mg montelukast once daily

Regular low dose ICS/LABA plus LAMA (N = 29)

160/4.5 mcg budesonide/formoterol combination inhaler, two inhalations once daily plus 5 mcg tiotropium once daily

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA + montelukast (N = 28)	Regular low dose ICS/LABA plus LAMA (N = 29)
% Female Sample size	n = 16 ; % = 57	n = 16 ; % = 55
Mean age (SD) Mean (SD)	51 (12)	55 (14)

Characteristic	Regular low dose ICS/LABA + montelukast (N = 28)	Regular low dose ICS/LABA plus LAMA (N = 29)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control AQLQ score (symptom domain) Mean (SD)	5.6 (1)	5.5 (1.1)
Lung function (% of predicted) FEV1 Mean (SD)	70 (9.7)	72.6 (10)

Outcomes

Study timepoints

- Baseline
- 48 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA + montelukast, Baseline, N = 28	Regular low dose ICS/LABA + montelukast, 48 week, N = 28	Regular low dose ICS/LABA plus LAMA, Baseline, N = 29	Regular low dose ICS/LABA plus LAMA, 48 week, N = 29
Quality of life (asthma quality of life questionnaire, symptom domain) Change scores, scale range 0-7 Mean (SD)	NA (NA)	0.5 (1)	NA (NA)	0.5 (1)
Lung Function (FEV1) (Percent of predicted) Change scores Mean (SD)	NA (NA)	5.4 (3.7)	NA (NA)	8.4 (3.4)
Inflammatory markers (FeNO) (ppb) Change scores Mean (SD)	NA (NA)	-5.6 (4.9)	NA (NA)	-2.8 (3.8)

Quality of life (asthma quality of life questionnaire, symptom domain) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better
Inflammatory markers (FeNO) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA + montelukast, Baseline, N = 28	Regular low dose ICS/LABA + montelukast, 48 week, N = 28	Regular low dose ICS/LABA plus LAMA, Baseline, N = 29	Regular low dose ICS/LABA plus LAMA, 48 week, N = 29
Severe asthma exacerbations Final values (calculated from	n = NA ; % = NA	n = 6 ; % = 20	n = NA ; % = NA	n = 5 ; % = 18

Outcome	Regular low dose ICS/LABA + montelukast, Baseline, N = 28	Regular low dose ICS/LABA + montelukast, 48 week, N = 28	Regular low dose ICS/LABA plus LAMA, Baseline, N = 29	Regular low dose ICS/LABA plus LAMA, 48 week, N = 29
reported percentages and rounded to nearest whole number) No of events				

Severe asthma exacerbations - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Qualityoflife(asthmaqualityoflifequestionnaire,symptomdomain)-MeanSD-Regular low-dose ICS/LABA + montelukast-Regular low-dose ICS/LABA plus LAMA-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on statistical methods used, switching rates between study arms, 15% dropout rate with no information on rates per arm or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular low-dose ICS/LABA + montelukast-Regular low-dose ICS/LABA plus LAMA-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on statistical methods used, switching rates between study arms, 15% dropout rate with no information on rates per arm or reasons for discontinuation)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Inflammatorymarkers(FeNO)-MeanSD-Regular low-dose ICS/LABA + montelukast-Regular low-dose ICS/LABA plus LAMA-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on statistical methods used, switching rates between study arms, 15% dropout rate with no information on rates per arm or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular low-dose ICS/LABA + montelukast-Regular low-dose ICS/LABA plus LAMA-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on statistical methods used, switching rates between study arms, 15% dropout rate with no information on rates per arm or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

Huchon, 2009

Bibliographic Reference	Huchon, G; Magnussen, H; Chuchalin, A; Dymek, L; Gonod, F Bonnet; Bousquet, J; Lung function and asthma control with beclomethasone and formoterol in a single inhaler.; Respiratory medicine; 2009; vol. 103 (no. 1); 41-9

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00476268
Study type	Randomised controlled trial (RCT)
Study location	Belgium, France, Hungary, Poland, Romania and Russia
Study setting	No additional information
Study dates	February 2004 - January 2005
Sources of funding	Funded by Chiesi Farmaceutici SpA
Inclusion criteria	Men and non-pregnant women aged 18-70 years Diagnosis of moderate to severe persistent asthma according to GINA FEV1 40-80% of predicted with an increase >12% and >200 mL after receiving SABA

	Received beclomethasone dipropionate 750-1000 mcg per day, or equivalent either alone or with a long-acting b2 agonist (formoterol 24 mcg or salmeterol 100 mcg per day), plus daily use of a short-acting beta-agonist for at least 2 months Symptoms >3 times during the week before study entry
Exclusion criteria	Smoked >20 cigarettes a day for 10 years
Recruitment / selection of participants	No additional information
Intervention(s)	Following a two-week run-in period where participants continued with their current asthma treatment, those allocated to the intervention received one of two treatments: • 100/6 mcg beclomethasone dipropionate/formoterol, plus a placebo, two puffs of each twice per day • 250 mcg beclomethasone dipropionate, two puffs, plus 6 mcg formoterol, one puff, plus a placebo, two puffs, each twice per day *Two study arms were combined for this review*
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Following a two-week run-in period where participants continued with their current asthma treatment, those allocated to the comparator received 250 mcg beclomethasone dipropionate plus placebo, both taken as two inhalations twice per day
Number of participants	645 randomised

	432 allocated to ICS/LABA, 403 completed 213 allocated to ICS, 193 completed
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	Efficacy data used modified intention to treat, including those who received at least one dose of the study drug and provided at least one follow-up measurement, and per protocol analysis Safety data used modified intention to treat, including those who received at least one dose of the study drug Missing data imputed using last observation carried forward

Study arms

Regular moderate/high dose ICS/LABA (N = 432)

100/6 mcg beclomethasone dipropionate/formoterol in a single inhaler, or 250 mcg beclomethasone dipropionate and 6 mcg formoterol in separate inhalers, all taken as two inhalations twice per day *Two study arms containing combination and concurrent ICS + LABA combined for this review*

Regular high dose ICS (N = 213)

250 mcg beclomethasone dipropionate, two inhalations twice per day, plus placebo

Characteristics

Arm-level characteristics

Characteristic	Regular moderate/high dose ICS/LABA (N = 432)	Regular high dose ICS (N = 213)
% Female Sample size	n = 281 ; % = 65	n = 134 ; % = 62.9

Characteristic	Regular moderate/high dose ICS/LABA (N = 432)	Regular high dose ICS (N = 213)
Mean age (SD) Mean (SD)	47.4 (12.3)	47.3 (13.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose (µg/day) Mean (SD)	662.6 (206.1)	681.45 (226.97)
Asthma control (Puffs per day) Daily SABA use Mean (SD)	0.7 (1.27)	0.57 (1.2)
Lung function (% of predicted) FEV1 Mean (SD)	65.4 (10.93)	65.3 (10.64)

Outcomes

Study timepoints

- Baseline
- 24 week

Dichotomous Outcomes

Outcome	Regular moderate/high dose ICS/LABA, Baseline, N = 432	Regular moderate/high dose ICS/LABA, 24 week, N = 432	Regular high dose ICS, Baseline, N = 213	Regular high dose ICS, 24 week, N = 213
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 11 ; % = 2.5	n = NA ; % = NA	n = 9 ; % = 4.2

Severe asthma exacerbations - Polarity - Lower values are better

Continuous Outcomes

Outcome	Regular moderate/high dose ICS/LABA, Baseline, N = 432	Regular moderate/high dose ICS/LABA, 24 week, N = 431	Regular high dose ICS, Baseline, N = 213	Regular high dose ICS, 24 week, N = 212
Lung Function (FEV1) (Litres) Final values Mean (SD)	1.97 (0.55)	2.23 (0.52)	1.97 (0.56)	2.13 (0.53)
Lung function (PEF) (Litres per minute) Final values Mean (SD)	314.2 (104.2)	335.85 (74.24)	303.52 (105.73)	309.41 (78.42)

Lung Function (FEV1) - Polarity - Higher values are better

Lung function (PEF) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate/high dose ICS/LABA-Regular high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate/high dose ICS/LABA-Regular high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(PEF)-MeanSD-Regular moderate/high dose ICS/LABA-Regular high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence to treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Ind, 2003

Bibliographic Reference	Ind, P W; Dal Negro, R; Colman, N C; Fletcher, C P; Browning, D; James, M H; Addition of salmeterol to fluticasone propionate treatment in moderate-to-severe asthma.; Respiratory medicine; 2003; vol. 97 (no. 5); 555-62

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Multinational - UK, Italy, Canada, Denmark, Iceland and the Republic of Ireland
Study setting	Hospitals and primary care centres
Study dates	January 1995 - November 1996
Sources of funding	Funded by GlaxoWellcome
Inclusion criteria	Aged 16-75 years Symptomatic asthma whilst receiving 500-800 mcg beclomethasone twice daily PEF <85% of post-bronchodilator PEF

	At least two exacerbations leading to a change in therapy or hospitalisation in the past year, with at least one in the past 6 months Diurnal PEF variability >15% and sub-optimal PEF (<90% of post-bronchodilator value) over the last 10 days of the run-in
Exclusion criteria	Receiving continuous oral corticosteroids Serious uncontrolled systemic disease
Recruitment / selection of participants	Recruited from 100 centres, method not reported
Intervention(s)	Following a 4-week run-in period where participants received 250 mcg fluticasone propionate twice daily, those allocated to the ICS/LABA arm received 250/50 mcg fluticasone propionate/salmeterol, one inhalation twice per day. All participants were provided with salbutamol to be used as-needed for symptom relief and a supply of oral prednisolone for use in an exacerbation.
Population subgroups	**Exacerbations** Yes - at least 2 in the past year **Atopy** Not reported
Comparator	Following a 4-week run-in period where participants received 250 mcg fluticasone propionate twice daily, those allocated to the ICS arm received one of two treatment options • 250mcg fluticasone propionate, one inhalation twice per day • 500mcg fluticasone propionate, one inhalation twice per day

	All participants were provided with salbutamol to be used as-needed for symptom relief and a supply of oral prednisolone for use in an exacerbation *Two study arms containing different ICS doses combined for this review*
Number of participants	496 randomised 171 allocated to ICS/LABA, 144 completed 325 allocated to ICS, 288 completed
Duration of follow-up	24 weeks
Indirectness	Downgraded by one increment due to population indirectness - 2% receiving anti-allergics, 6% receiving anticholinergics, 10% receiving xanthines
Additional comments	ITT

Study arms

Regular moderate dose ICS/LABA (N = 171)
50/250 mcg fluticasone propionate/salmeterol, one inhalation twice per day

Regular moderate/high dose ICS (N = 325)
250 or 500 mcg fluticasone propionate, one inhalation twice per day *Two study arms containing different ICS doses combined for this review*

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 171)	Regular moderate/high dose ICS (N = 325)
% Female Sample size	n = 101 ; % = 59	n = 165 ; % = 51
Mean age (SD) Mean (SD)	44.8 (15.6)	44.8 (15.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Median Nominal	NA	NA
BUD/BDP Nominal	1000	1000
FP Nominal	500	625

Characteristic	Regular moderate dose ICS/LABA (N = 171)	Regular moderate/high dose ICS (N = 325)
Asthma control Exacerbations in past year requiring oral corticosteroids Sample size	n = NA ; % = NA	n = NA ; % = NA
Zero Sample size	n = 59 ; % = 35	n = 104 ; % = 32
one Sample size	n = 54 ; % = 32	n = 104 ; % = 32
> One Sample size	n = 57 ; % = 34	n = 116 ; % = 36
Lung function (Litres) FEV1 Mean (SD)	2.3 (0.9)	2.3 (0.9)

Outcomes

Study timepoints

- Baseline
- 24 week

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 171	Regular moderate dose ICS/LABA, 24 week, N = 171	Regular moderate/high dose ICS, Baseline, N = 325	Regular moderate/high dose ICS, 24 week, N = 325
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 47 ; % = 27	n = NA ; % = NA	n = 107 ; % = 33

Severe asthma exacerbations - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information on randomisation method used or adherence to study medication and 13% dropout rate with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Jenkins, 2000

Bibliographic Reference	Jenkins, C; Woolcock, A J; Saarelainen, P; Lundback, B; James, M H; Salmeterol/fluticasone propionate combination therapy 50/250 microg twice daily is more effective than budesonide 800 microg twice daily in treating moderate to severe asthma.; Respiratory medicine; 2000; vol. 94 (no. 7); 715-23

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by Glaxo Wellcome
Inclusion criteria	≥12 years of age Documented history of reversible airway obstruction

	Receiving 800-1200 mcg/day of beclomethasone or budesonide or 400-600 mcg/day fluticasone propionate for ≥4 weeks FEV1 >50% or PEF <85% predicted during run-in >15% increase in FEV1 after receiving SABA SABA use more than twice daily, or had a total daily symptom score ≥2 on ≥4 out of 7 days of run-in
Exclusion criteria	Acute exacerbation requiring hospitalisation within 4 weeks Received oral, parenteral or depot corticosteroids within 4 weeks Had a lower respiratory tract infection or change in asthma medication within 4 weeks Treatment with a LABA, or slow-releasing bronchodilator within 2 weeks Smoking history ≥10 pack years Pregnant or lactating females
Recruitment / selection of participants	Recruited from 44 centres, method not reported
Intervention(s)	Following a 2-week run-in period where all medication except regular ICS and SABA was withdrawn, participants randomised to the ICS/LABA arm received 50/250 mcg salmeterol/fluticasone propionate plus placebo, twice daily. Participants were also provided with a salbutamol inhaler for symptom relief.
Population subgroups	Exacerbations Not reported

	Atopy Not reported
Comparator	Following a 2-week run-in period where all medication except regular ICS and SABA was withdrawn, participants randomised to the ICS arm received 800 mcg budesonide plus placebo, twice daily. Participants were also provided with a salbutamol inhaler for symptom relief.
Number of participants	353 randomised 180 received ICS/LABA 173 received ICS monotherapy
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	Intention to treat

Study arms

Regular moderate dose ICS/LABA (N = 180)
50/250 mcg salmeterol/fluticasone propionate plus placebo, twice daily

Regular high dose ICS (N = 173)
800 mcg budesonide plus placebo, twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 180)	Regular high dose ICS (N = 173)
% Female Sample size	n = 90 ; % = 50	n = 86 ; % = 50
Mean age (SD) Nominal	45	48
Mean age (SD) Range	16 to 75	14 to 80
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Median Nominal	NA	NA
Fluticasone propionate Nominal	500	500
Budesonide Nominal	800	800

Characteristic	Regular moderate dose ICS/LABA (N = 180)	Regular high dose ICS (N = 173)
Beclomethasone dipropionate Nominal	1000	1000
Asthma control Nominal	NR	NR
Lung function (% of predicted) Mean (range) FEV1 Nominal	68	72
Lung function (% of predicted) Mean (range) FEV1 Range	33 to 105	37 to 109

Outcomes

Study timepoints

- Baseline
- 24 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 173	Regular moderate dose ICS/LABA, 24 week, N = 173	Regular high dose ICS, Baseline, N = 165	Regular high dose ICS, 24 week, N = 165
Lung function (mean morning PEF over treatment period) (Litres per	399 (41.3)	406 (48.3)	374 (41.9)	380 (48.9)

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 173	Regular moderate dose ICS/LABA, 24 week, N = 173	Regular high dose ICS, Baseline, N = 165	Regular high dose ICS, 24 week, N = 165
minute) Final values Mean (SD)				

Lung function (mean morning PEF over treatment period) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 180	Regular moderate dose ICS/LABA, 24 week, N = 180	Regular high dose ICS, Baseline, N = 173	Regular high dose ICS, 24 week, N = 173
Severe asthma exacerbations Final values (defined as requiring deterioration requiring hospitalisation) No of events	n = NA ; % = NA	n = 1 ; % = 0.6	n = NA ; % = NA	n = 2 ; % = 1
Pneumonia Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0

Severe asthma exacerbations - Polarity - Lower values are better

Pneumonia - Polarity - Lower values are better

Contrast Outcomes

Outcome	Regular moderate dose ICS/LABA vs Regular high dose ICS, Baseline, N2 = NA, N1 = NA	Regular moderate dose ICS/LABA vs Regular high dose ICS, 24 week, N2 = 173, N1 = 165
Lung Function (FEV1) (Litres) Final values Mean (95% CI)	NA (NA to NA)	0.091 (0 to 0.17)

Lung Function (FEV1) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Lungfunction(meanmorningPEFovertreatmentperiod)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence not monitored and 17% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence not monitored and 17% dropout rate with discontinuation reasons related to participant's health status)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-LungFunction(FEV1)-MeanNineFivePercentCI-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence not monitored and 17% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia-NoOfEvents-Regular moderate dose ICS/LABA-Regular high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, adherence not monitored and 17% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Juniper, 2002

Bibliographic Reference	Juniper, Elizabeth F; Jenkins, Christine; Price, Martin J; James, Mark H; Impact of inhaled salmeterol/fluticasone propionate combination product versus budesonide on the health-related quality of life of patients with asthma.; American journal of respiratory medicine : drugs, devices, and other interventions; 2002; vol. 1 (no. 6); 435-40

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Belgium, the Netherlands, Australia and South Africa
Study setting	No additional information
Study dates	No additional information
Sources of funding	Sponsored by GlaxoSmithKline
Inclusion criteria	≥12 years of age Receiving inhaled beclomethasone or budesonide at a dose of 800-1200 mcg per day or fluticasone propionate at a dose of 400-600 mcg per day for at least 4 weeks

Exclusion criteria	Lower respiratory tract infection, exacerbation, change in asthma medication or systemic corticosteroid use within 4 weeks Smoking history >10 pack years Received LABA or slow-release bronchodilator within 2 weeks FEV1 50-85% of predicted or mean morning PEF 50-85% of predicted over 7 days ≥15% increase in FEV1 after receiving SABA Total symptom score ≥2 on ≥4 of the last 7 days of the run-in, or use of albuterol on >2 occasions per day on ≥4 of the last 7 days
Recruitment / selection of participants	Recruited from 26 centres, method not reported
Intervention(s)	Following a 2-week run-in period where participants continued to use their usual ICS therapy, those randomised to the intervention received 50/250 mcg salmeterol/fluticasone propionate (Seretide/Advair), one inhalation twice a day via a Diskus inhaler plus a placebo Turbuhaler
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Following a 2-week run-in period where participants continued to use their usual ICS therapy, those randomised to the comparator received 800 mcg budesonide, one inhalation twice a day via a Turbuhaler plus a placebo Diskus inhaler

Number of participants	144 randomised, 113 completed 55 received and completed ICS/LABA 58 received and completed ICS
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Per protocol analysis

Study arms

Regular moderate dose ICS/LABA (N = 55)

50/250 mcg salmeterol/fluticasone propionate, one inhalation twice daily

Regular high dose ICS (N = 58)

800 mcg budesonide, one inhalation twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 55)	Regular high dose ICS (N = 58)
% Female Sample size	n = 23 ; % = 42	n = 29 ; % = 50
Mean age (SD) Mean (SD)	50 (15)	51 (15)

Characteristic	Regular moderate dose ICS/LABA (N = 55)	Regular high dose ICS (N = 58)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 52 ; % = 95	n = 55 ; % = 95
Other Sample size	n = 3 ; % = 5	n = 3 ; % = 5
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Nominal	68	72
Lung function (% of predicted) FEV1 Range	33 to 105	37 to 109

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 55	Regular moderate dose ICS/LABA, 12 week, N = 55	Regular high dose ICS, Baseline, N = 58	Regular high dose ICS, 12 week, N = 58
Quality of life (AQLQ) Change scores, scale range: 1-7 Mean (SD)	NA (NA)	0.89 (0.82)	NA (NA)	0.44 (0.76)

Quality of life (AQLQ) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Qualityoflife(AQLQ)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, no adherence monitoring included and 22% missing outcome data with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Katial, 2011

Bibliographic Reference	Katial, Rohit K; Bernstein, David; Prazma, Charlene M; Lincourt, William R; Stempel, David A; Long-term treatment with fluticasone propionate/salmeterol via Diskus improves asthma control versus fluticasone propionate alone.; Allergy and asthma proceedings; 2011; vol. 32 (no. 2); 127-36

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	ADA109055
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	≥12 years of age Diagnosis of asthma for ≥6 months

	FEV1 50-85% predicted FEV1 reversibility >12% after receiving SABA Treated with low-moderate dose of ICS or ICS/LABA for ≥4 weeks prior to screening Symptomatic whilst taking medication in the 4 weeks prior to screening Asthma symptom score ≥1 on ≥2 days and SABA use on any 2 or more days during any single week of the run-in
Exclusion criteria	Life-threatening asthma in the past year Seasonal or exercise induced asthma without other manifestations of persistent asthma Concurrent respiratory disease or any other significant disease/condition Worsening asthma within 4 weeks (ER visit, use of oral/parenteral corticosteroids)
Recruitment / selection of participants	Recruited from centres in Argentina, Brazil, USA, Canada and the Philippines - method not reported
Intervention(s)	Following a 2-3 week run-in where participants received open-label 100 mcg fluticasone propionate twice daily, those randomised to the ICS/LABA arm received 250/50 mcg fluticasone/salmeterol twice daily.
Population subgroups	<u>Exacerbations</u> Not reported <u>Atopy</u> Majority atopic: ICS/LABA n= 181 (60%), ICS n= 194 (62%)

Comparator	Following a 2-3 week run-in where participants received open-label 100 mcg fluticasone propionate twice daily, those randomised to the ICS arm received 250 fluticasone twice daily.
Number of participants	621 randomised 306 received ICS/LABA, 225 completed 315 received ICS monotherapy, 242 completed
Duration of follow-up	52 weeks
Indirectness	None
Additional comments	Intention to treat

Study arms

Regular moderate dose ICS/LABA (N = 306)

50/250 mcg salmeterol/fluticasone propionate twice daily

Regular moderate dose ICS (N = 315)

250 mcg fluticasone propionate twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 306)	Regular moderate dose ICS (N = 315)
% Female Sample size	n = 190 ; % = 62	n = 202 ; % = 64
Mean age (SD)	36.8 (15.5)	39.3 (15.5)

Characteristic	Regular moderate dose ICS/LABA (N = 306)	Regular moderate dose ICS (N = 315)
Mean (SD)		
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 196 ; % = 64	n = 208 ; % = 66
Black Sample size	n = 64 ; % = 21	n = 60 ; % = 19
Asian Sample size	n = 40 ; % = 13	n = 41 ; % = 13
Other Sample size	n = 6 ; % = 2	n = 6 ; % = 2
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1	68.9 (9.9)	69 (9.6)

Characteristic	Regular moderate dose ICS/LABA (N = 306)	Regular moderate dose ICS (N = 315)
Mean (SD)		

Outcomes

Study timepoints

- Baseline
- 52 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 306	Regular moderate dose ICS/LABA, 52 week, N = 306	Regular moderate dose ICS, Baseline, N = 315	Regular moderate dose ICS, 52 week, N = 315
Lung Function (FEV1) (Percent of predicted) Final values Mean (SD)	74 (NR)	81.2 (20.5)	73 (NR)	75.9 (17.6)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	23.6 (43.2)	NA (NA)	9.8 (42.6)
Reliever/rescue medication use (SABA free days) (percent) Change scores Mean (SD)	NA (NA)	38.6 (36)	NA (NA)	29.4 (31.9)

Lung Function (FEV1) - Polarity - Higher values are better

Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use (SABA free days) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 306	Regular moderate dose ICS/LABA, 52 week, N = 306	Regular moderate dose ICS, Baseline, N = 315	Regular moderate dose ICS, 52 week, N = 315
Severe asthma exacerbations Number of participants with at least one exacerbations No of events	n = NA ; % = NA	n = 49 ; % = 12	n = NA ; % = NA	n = 83 ; % = 23

Severe asthma exacerbations - Polarity - Lower values are better

Contrast Outcomes

Outcome	Regular moderate dose ICS/LABA vs Regular moderate dose ICS, Baseline, N2 = 315, N1 = 306	Regular moderate dose ICS/LABA vs Regular moderate dose ICS, 52 week, N2 = 315, N1 = 306
Severe exacerbation rate Final values, event rate per person year Mean (95% CI)	NA (NA to NA)	0.62 (0.42 to 0.92)

Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(25% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(morningPEF)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(25% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliever/rescuemedicationuse(SABAfreedays)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(25% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(25% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Severeexacerbationrate-MeanNineFivePercentCI-Regular moderate dose ICS/LABA-Regular moderate dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(25% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Kerstjens, 2015

Bibliographic Reference	Kerstjens, Huib A M; Casale, Thomas B; Bleecker, Eugene R; Meltzer, Eli O; Pizzichini, Emilio; Schmidt, Olaf; Engel, Michael; Bour, Loek; Verkleij, Cynthia B; Moroni-Zentgraf, Petra; Bateman, Eric D; Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials.; The Lancet. Respiratory medicine; 2015; vol. 3 (no. 5); 367-76

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	MezzoTinA-asthma-1 and MezzoTinAasthma-2 - NCT01172808 and NCT01172821
Study type	Randomised controlled trial (RCT)
Study location	Multinational - Latvia, Poland, Romania, Russia, Brazil, China, Colombia, Germany, Guatemala, India, Japan, Mexico, Peru and the USA
Study setting	No additional information
Study dates	August 2010 - November 2012
Sources of funding	Funded by Boehringer Ingelheim
Inclusion criteria	Aged 18-75 years

	Diagnosed with asthma before the age of 40, and at least 3 months before enrolment ≥12% and 200 mL FEV1 reversibility after receiving SABA Symptomatic, defined by an ACQ score >1.5 FEV1 60-90% of predicted at screening, and within 30% of screening value at randomisation Receiving stable moderate-dose ICS (400-800 mcg budesonide equivalent) alone or in combination with LABA/SABA for at least 4 weeks Non-smoking for at least one-year with a history <10 pack years
Exclusion criteria	Present or past diagnosis of COPD Serious co-existing disease Concurrent use of long acting anticholinergics or beta-blockers within 4 weeks
Recruitment / selection of participants	Recruited from 233 centres, method not reported
Intervention(s)	Following a 4-week run-in period, participants allocated to the ICS/LABA arm received 50 mcg salmeterol twice daily in addition to their regular ICS therapy
Population subgroups	**Exacerbations** Not reported

	Atopy Not reported
Comparator	Following a 4-week run-in period, participants allocated to the ICS + LAMA arm received 2.5 or 5 mcg tiotropium, taken once daily in the evening, in addition to their usual ICS therapy *Study had two arms containing 2.5 and 5 mcg tiotropium per day, combined for this review, as well as a placebo arm which was excluded due to not containing a relevant intervention*
Number of participants	2103 randomised 541 received ICS/LABA, 509 completed 519 received 2.5 mcg tiotropium, 483 completed 520 received 5 mcg tiotropium, 495 completed 523 received placebo (excluded from this review)
Duration of follow-up	24 weeks
Indirectness	Downgraded by one increment due to population indirectness - 9% of participants were treated with leukotriene modifiers at screening
Additional comments	ITT

Study arms

Regular moderate dose ICS/LABA (N = 541)

Usual ICS therapy plus 50 mcg salmeterol twice per day

Regular moderate dose ICS plus LAMA (N = 1036)
Usual ICS therapy plus either 2.5 or 5 mcg tiotropium once per day *Study contained two arms containing 2.5 and 5 mcg per day, combined for this review*

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 541)	Regular moderate dose ICS plus LAMA (N = 1036)
% Female Sample size	n = 312 ; % = 58	n = 616 ; % = 59
Mean age (SD) Mean (SD)	42.1 (12.9)	43.9 (12.8)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Mean (SD)	650.8 (205.2)	659.9 (214.6)
Asthma control ACQ-7 Mean (SD)	2.15 (0.47)	2.19 (0.49)
Lung function (% of predicted) FEV1	73 (8.3)	72.5 (8.3)

Characteristic	Regular moderate dose ICS/LABA (N = 541)	Regular moderate dose ICS plus LAMA (N = 1036)
Mean (SD)		

Outcomes

Study timepoints

- Baseline
- 24 week

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 541	Regular moderate dose ICS/LABA, 24 week, N = 541	Regular moderate dose ICS plus LAMA, Baseline, N = 1036	Regular moderate dose ICS plus LAMA, 24 week, N = 1036
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 34 ; % = 6	n = NA ; % = NA	n = 53 ; % = 5
Pneumonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 5 ; % = 1	n = NA ; % = NA	n = 12 ; % = 1
Adverse events Final values No of events	n = NA ; % = NA	n = 289 ; % = 57	n = NA ; % = NA	n = 586 ; % = 59

Severe asthma exacerbations - Polarity - Lower values are better
Pneumonia (respiratory tract infections) - Polarity - Lower values are better

Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular low-moderate dose ICS plus LAMA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia(respiratorytractinfections)-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular low-moderate dose ICS plus LAMA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No adherence monitoring included)*
Overall bias and Directness	Overall Directness	Indirectly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular low-moderate dose ICS plus LAMA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

Kerstjens, 2020

Bibliographic Reference	Kerstjens, Huib A M; Maspero, Jorge; Chapman, Kenneth R; van Zyl-Smit, Richard N; Hosoe, Motoi; Tanase, Ana-Maria; Lavecchia, Catherine; Pethe, Abhijit; Shu, Xu; D'Andrea, Peter; Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study.; The Lancet. Respiratory medicine; 2020; vol. 8 (no. 10); 1000-1012

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	IRIDIUM - NCT02571777
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	Private clinics, universities and hospitals
Study dates	December 2015 - June 2019
Sources of funding	Funded by Novaritis
Inclusion criteria	Aged 18-75 years

	Diagnosed with asthma for at least one-year FEV1 <80% of predicted and ≥12% or 200 mL increase after receiving SABA Symptomatic during run-in, with an ACQ score >1.5 History of at least one exacerbation that required medical attention and systemic corticosteroids in the past year Receiving moderate-high dose ICS/LABA for at least 3 months, and at a stable dos for a month
Exclusion criteria	Smoking within 6 months, or a history >10 pack years Chronic lung disease other than asthma Asthma exacerbation requiring systemic corticosteroids within 6 months Respiratory tract infection or asthma worsening within a month
Recruitment / selection of participants	Recruited from 415 sites, method not reported
Intervention(s)	Following a 2-week run-in period where participants received 250/50 mcg fluticasone propionate/salmeterol twice daily, those allocated to the ICS/LABA plus LAMA arm received one of two therapies: • 80/150/50 mcg mometasone furoate/indacaterol/glycopyrronium once daily • 160/150/50 mcg mometasone furoate/indacaterol/glycopyrronium once daily Salbutamol was available throughout for use as-needed for symptom relief

Population subgroups	**Exacerbations** Yes - all had at least one within the year **Atopy** Not reported
Comparator	Following a 2-week run-in period where participants received 250/50 mcg fluticasone propionate/salmeterol twice daily, those allocated to the ICS/LABA arm received one of two therapies: • 320/150 mcg mometasone furoate/indacaterol once daily • 500/50 fluticasone propionate/salmeterol twice daily Salbutamol was available throughout for use as-needed for symptom relief *Study also included an arm containing 160/150 mcg mometasone furoate/indacaterol, excluded from this review due to not containing a moderate-high dose ICS/LABA combination*
Number of participants	3092 randomised 1239 allocated to ICS/LABA + LAMA, 1100 completed 1236 allocated to ICS/LABA, 1104 completed 617 allocated to low-dose ICS/LABA (excluded from this review)
Duration of follow-up	52 weeks
Indirectness	None

Additional comments	ITT

Study arms

Regular low dose ICS/LABA + LAMA (N = 1239)

80/150/50 or 160/150/50 mometasone furoate/indacaterol/glycopyrronium combination inhaler, one inhalation once daily *two study arms containing different doses combined for this review*

Regular moderate/high dose ICS/LABA (N = 1236)

320/150 mcg mometasone furoate/indacaterol once daily or 500/50 mcg fluticasone propionate/salmeterol twice daily *Two study arms containing different ICS/LABA combinations combined for this review*

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS/LABA + LAMA (N = 1239)	Regular moderate/high dose ICS/LABA (N = 1236)
% Female Sample size	n = 743 ; % = 60	n = 797 ; % = 64
Mean age (SD) Mean (SD)	52.25 (12.81)	52.45 (12.53)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Characteristic	Regular low dose ICS/LABA + LAMA (N = 1239)	Regular moderate/high dose ICS/LABA (N = 1236)
ICS dose Previous treatment Sample size	n = NA ; % = NA	n = NA ; % = NA
Moderate-dose ICS/LABA Sample size	n = 765 ; % = 62	n = 773 ; % = 63
High-dose ICS/LABA Sample size	n = 463 ; % = 37	n = 457 ; % = 37
Low-dose ICS/LABA or no ICS/LABA Sample size	n = 6 ; % = 0	n = 4 ; % = 0
Asthma control ACQ-7 Mean (SD)	2.5 (0.6)	2.6 (0.6)
Lung function (% of predicted) FEV1 Mean (SD)	54.6 (13.9)	54.9 (13.5)

Outcomes

Study timepoints

- Baseline
- 52 week

Continuous Outcomes

Outcome	Regular low dose ICS/LABA + LAMA, Baseline, N = 1239	Regular low dose ICS/LABA + LAMA, 52 week, N = 1239	Regular moderate/high dose ICS/LABA, Baseline, N = 1236	Regular moderate/high dose ICS/LABA, 52 week, N = 1236
Reliever medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-0.85 (1.43)	NA (NA)	-0.8 (1.42)
Reliever medication use (SABA-free days) (%) Change scores Mean (SD)	NA (NA)	23.46 (32.75)	NA (NA)	23.35 (32.7)
Quality of life (Asthma Quality of Life Questionnaire) Change scores, scale range: 1-7 Mean (SD)	NA (NA)	0.82 (0.84)	NA (NA)	0.83 (0.84)

Reliever medication use - Polarity - Lower values are better
Reliever medication use (SABA-free days) - Polarity - Higher values are better
Quality of life (Asthma Quality of Life Questionnaire) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS/LABA + LAMA, Baseline, N = 1239	Regular low dose ICS/LABA + LAMA, 52 week, N = 1239	Regular moderate/high dose ICS/LABA, Baseline, N = 1236	Regular moderate/high dose ICS/LABA, 52 week, N = 1239
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 285 ; % = 23	n = NA ; % = NA	n = 324 ; % = 26
Mortality Final values No of events	n = NA ; % = NA	n = 3 ; % = 0	n = NA ; % = NA	n = 4 ; % = 0
Pneumonia Final values No of events	n = NA ; % = NA	n = 5 ; % = 0	n = NA ; % = NA	n = 6 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 918 ; % = 74	n = NA ; % = NA	n = 941 ; % = 76

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Pneumonia - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Relievermedicationuse-MeanSD-Regular low-moderate dose ICS/LABA + LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and 12% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Relievermedicationuse(SABA-freedays)-MeanSD-Regular low-moderate dose ICS/LABA + LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and 12% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Qualityoflife(AsthmaQualityofLifeQuestionnaire)-MeanSD-Regular low-moderate dose ICS/LABA + LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and 12% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular low-moderate dose ICS/LABA + LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and 12% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular low-moderate dose ICS/LABA + LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and 12% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia-NoOfEvents-Regular low-moderate dose ICS/LABA + LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and 12% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular low-moderate dose ICS/LABA + LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No adherence monitoring included and 12% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Kerwin, 2011

Bibliographic Reference	Kerwin, E.; Prazma, C.M.; Sutton, L.; Stempel, D.A.; Safety and efficacy of long-term treatment with fluticasone propionate and salmeterol via DISKUS versus fluticasone propionate alone; Clinical Research and Regulatory Affairs; 2011; vol. 28 (no. 1); 14-21

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	ClinicalTrials.gov identifier: NCT00452348
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	≥12 years of age Diagnosis of asthma for ≥6 months

	FEV1 50-85% predicted FEV1 reversibility ≥12% after receiving SABA Receiving moderate-low dose ICS or low-dose ICS/LABA combination for ≥4 weeks prior to screening Asthma symptom score ≥1 on ≥2 days and SABA use on ≥2 days during run-in
Exclusion criteria	Life threatening asthma within a year Seasonal or exercise-induced asthma without other manifestations of persistent asthma Concurrent respiratory disease or any significant other disease/condition Worsening asthma within 4 weeks (defined as ER treatment, hospitalisation or use of oral/parenteral corticosteroids)
Recruitment / selection of participants	Recruited from USA, Canada, Argentina, Brazil and the Philippines
Intervention(s)	Following a 2-3 week run-in period where participants received open label 100 mcg fluticasone propionate twice daily, those randomised to the ICS/LABA arm received 250/50 mcg fluticasone propionate/salmeterol twice daily
Population subgroups	Exacerbations Not reported Atopy Not reported

Comparator	Following a 2-3 week run-in period where participants received open label 100 mcg fluticasone propionate twice daily, those randomised to the ICS arm received 250 mcg fluticasone propionate twice daily
Number of participants	628 randomised, 465 completed 310 received ICS/LABA 318 received ICS
Duration of follow-up	52 weeks
Indirectness	None
Additional comments	Intention to treat

Study arms

Regular moderate dose ICS/LABA (N = 310)

250/50 mcg fluticasone propionate/salmeterol twice daily

Regular moderate dose ICS (N = 318)

250 mcg fluticasone twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 310)	Regular moderate dose ICS (N = 318)
% Female Sample size	n = 186 ; % = 60	n = 181 ; % = 57
Mean age (SD)	40.9 (15.7)	39.6 (16.6)

Characteristic	Regular moderate dose ICS/LABA (N = 310)	Regular moderate dose ICS (N = 318)
Mean (SD)		
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 254 ; % = 82	n = 261 ; % = 82
African American Sample size	n = 28 ; % = 9	n = 25 ; % = 8
Asian Sample size	n = 19 ; % = 6	n = 25 ; % = 8
Other Sample size	n = 9 ; % = 3	n = 6 ; % = 2
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1	69.1 (9.9)	69.7 (9.9)

Characteristic	Regular moderate dose ICS/LABA (N = 310)	Regular moderate dose ICS (N = 318)
Mean (SD)		

Outcomes

Study timepoints

- Baseline
- 52 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 310	Regular moderate dose ICS/LABA, 52 week, N = NR	Regular moderate dose ICS, Baseline, N = 318	Regular moderate dose ICS, 52 week, N = NR
Asthma Control (Asthma Control Test) Change scores. scale range 0-25 Mean (SD)	NA (NA)	4.7 (4)	NA (NA)	3.9 (4.5)
Lung Function (FEV1) (% of predicted) Change scores Mean (SD)	NA (NA)	5.2 (9.7)	NA (NA)	3.7 (10.5)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	27.7 (50.18)	NA (NA)	14.6 (44.4)

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 310	Regular moderate dose ICS/LABA, 52 week, N = NR	Regular moderate dose ICS, Baseline, N = 318	Regular moderate dose ICS, 52 week, N = NR
Reliever/rescue medication use (SABA-free days) (%) Change scores Mean (SD)	NA (NA)	38.6 (35.04)	NA (NA)	27.7 (32.1)
Severe exacerbation rate Final values, total number of events Nominal	NA	75	NA	87

Asthma Control (Asthma Control Test) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use (SABA-free days) - Polarity - Higher values are better
Severe exacerbation rate - Polarity - Lower values are better
163 participants dropped-out before 52-weeks - not reported which study arms this was from. Analysed using intention to treat.

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 310	Regular moderate dose ICS/LABA, 52 week, N = NR	Regular moderate dose ICS, Baseline, N = 318	Regular moderate dose ICS, 52 week, N = NR
Severe asthma exacerbations Number of participants with at least one event (number calculated from percentage reported in paper) No of events	n = NA ; % = NA	n = 59 ; % = 19	n = NA ; % = NA	n = 70 ; % = 22

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 310	Regular moderate dose ICS/LABA, 52 week, N = NR	Regular moderate dose ICS, Baseline, N = 318	Regular moderate dose ICS, 52 week, N = NR
Mortality No of events	n = NA ; % = NA	n = 1 ; % = 0.3	n = NA ; % = NA	n = 1 ; % = 0.3
Adverse events Final values No of events	n = NA ; % = NA	n = 242 ; % = 78	n = NA ; % = NA	n = 261 ; % = 82

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-AsthmaControl(AsthmaControlTest)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, no adherence monitoring included, 26% dropout rate, no information of rates per study arm, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, no adherence monitoring included, 26% dropout rate, no information of rates per study arm, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, no adherence monitoring included, 26% dropout rate, no information of rates per study arm, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, no adherence monitoring included, 26% dropout rate, no information of rates per study arm, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, no adherence monitoring included, 26% dropout rate, no information of rates per study arm, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(PEF)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, no adherence monitoring included, 26% dropout rate, no information of rates per study arm, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliever/rescuemedicationuse(SABA-freedays)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, no adherence monitoring included, 26% dropout rate, no information of rates per study arm, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Severeexacerbationrate-Nominal-Regular moderate dose ICS/LABA-Regular moderate dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, no adherence monitoring included, 26% dropout rate, no information of rates per study arm, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Kuna, 2007

Bibliographic Reference	Kuna, P; Peters, M J; Manjra, A I; Jorup, C; Naya, I P; Martinez-Jimenez, N E; Buhl, R; Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations.; International journal of clinical practice; 2007; vol. 61 (no. 5); 725-36

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	COMPASS
Study type	Randomised controlled trial (RCT)
Study location	Not reported
Study setting	No additional information
Study dates	December 2003 - March 2005
Sources of funding	Funded by AstraZeneca
Inclusion criteria	Outpatients aged ≥12 years of age Diagnosis of asthma for ≥6 months

	Using ICS for ≥3 months and at a dose of ≥500 mcg/day (BUD or FP) or ≥1000 mcg/day (any other ICS) for ≥1 month FEV1 ≥50% predicted ≥12% FEV1 reversibility following SABA ≥1 asthma exacerbation in the previous year Using reliever medication on ≥5 days out of the last 7 during a 2-week run-in
Exclusion criteria	Used systemic corticosteroids, or had a respiratory tract infection within 30 days >10 rescue medication uses on any day of run-in Exacerbation during run-in
Recruitment / selection of participants	Not reported
Intervention(s)	Following a 2-week run-in where participants received regular ICS plus terbutaline, those randomised to regular ICS/LABA plus as-needed ICS/LABA received 160/4.5 mcg budesonide/formoterol, two inhalations twice daily, plus additional inhalations as-needed for symptom relief.
Population subgroups	<u>Exacerbations</u> All participants had at least one exacerbation in the past year

	Atopy Not reported
Comparator	Following a 2-week run-in where participants received regular ICS plus terbutaline, participants could have been randomised to one of two regular ICS/LABA study arms. One arm received 25/125 salmeterol/fluticasone, two inhalations twice daily, plus terbutaline as-needed for symptom relief. The other arm received 320/9 mcg budesonide/formoterol, one inhalation twice daily, plus terbutaline as-needed. *Two study arms were combined for this review due to intra-drug class comparisons not being made*
Number of participants	3335 randomised, 3172 completed 1107 received regular ICS/LABA plus as-needed ICS/LABA, 1052 completed 2228 received regular ICS/LABA plus SABA, 2120 completed
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	Intention to treat

Study arms

Low dose ICS/formoterol MART (N = 1107)

160/4.5 mcg budesonide/formoterol, one inhalation twice daily plus as-needed for symptom relief

Regular moderate dose ICS/LABA (N = 2228)
25/125 mcg salmeterol/fluticasone propionate, two inhalations twice daily plus terbutaline as-needed or 320/9 mcg budesonide/formoterol, one inhalation twice daily plus terbutaline as-needed *two regular ICS/LABA study arms combined for this review*

Characteristics

Arm-level characteristics

Characteristic	Low dose ICS/formoterol MART (N = 1107)	Regular moderate dose ICS/LABA (N = 2228)
% Female Sample size	n = 628 ; % = 57	n = 1296 ; % = 58
Mean age (SD) Mean (SD)	38 (17)	38 (17)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Mean (SD)	740 (240)	747 (246)
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1	72 (14)	73 (14)

Characteristic	Low dose ICS/formoterol MART (N = 1107)	Regular moderate dose ICS/LABA (N = 2228)
Mean (SD)		

Outcomes

Study timepoints

- Baseline
- 24 week

Dichotomous Outcomes

Outcome	Low dose ICS/formoterol MART, Baseline, N = 1107	Low dose ICS/formoterol MART, 24 week, N = 1107	Regular moderate dose ICS/LABA, Baseline, N = 2228	Regular moderate dose ICS/LABA, 24 week, N = 2228
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 94 ; % = 9	n = NA ; % = NA	n = 264 ; % = 12
Mortality Final values No of events	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better

Continuous Outcomes

Outcome	Low dose ICS/formoterol MART, Baseline, N = 1107	Low dose ICS/formoterol MART, 24 week, N = 1107	Regular moderate dose ICS/LABA, Baseline, N = 2228	Regular moderate dose ICS/LABA, 24 week, N = 2228
Severe exacerbation rate Final values, total number of events Nominal	NA	125	NA	381

Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular low-dose ICS/LABA + as-needed ICS/LABA-Regular moderate-high dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular low-dose ICS/LABA + as-needed ICS/LABA-Regular moderate-high dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Severeexacerbationrate-Nominal-Low dose ICS/formoterol MART-Regular moderate dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Lee, 2020

Bibliographic Reference	Lee, L.A.; Bailes, Z.; Barnes, N.; Boulet, L.-P.; Edwards, D.; Fowler, A.; Hanania, N.A.; Kerstjens, H.A.M.; Kerwin, E.; Nathan, R.; Oppenheimer, J.; Papi, A.; Pascoe, S.; Brusselle, G.; Peachey, G.; Sule, N.; Tabberer, M.; Pavord, I.D.; Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial; The Lancet. Respiratory medicine; 2020

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	CAPTAIN - NCT02924688
Study type	Randomised controlled trial (RCT)
Study location	No additional information
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	≥18 years of age

	Inadequately controlled asthma symptoms (ACQ score ≥1.5, documented healthcare contact or acute change in asthma therapy within a year) Receiving ICS/LABA for ≥12 weeks with no changes in dose for ≥6 weeks prior to screening FEV1 30-85% of predicted ≥12% and 200 mL FEV1 reversibility after receiving SABA
Exclusion criteria	COPD diagnosis Concurrent respiratory conditions, such as pneumonia and risk factors for pneumonia Current smokers and those with a history >10 pack years
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 3-week run-in period where participants received 250/50 fluticasone propionate/salmeterol twice daily, those randomised to the ICS/LABA plus LAMA arm received either 100/31.25/25 or 100/62.5/25 mcg fluticasone furoate//umeclidinium/vilanterol once daily *Two study arms containing two different doses combined for this review - two further study arms were excluded due to containing 200 mcg fluticasone furoate which does not represent low-moderate dose ICS*
Population subgroups	**Exacerbations** In past 12 months: 0=37%, 1=48%, ≥2=16% **Atopy**

	Not reported
Comparator	Following a 3-week run-in period where participants received 250/50 fluticasone propionate/salmeterol twice daily, those randomised to the ICS/LABA arm received either 100/25 or 200/25 fluticasone furoate/vilanterol once daily *Two study arms containing two different doses combined for this review*
Number of participants	2436 randomised 405 received 100/31.25/25 mcg ICS/LABA+LAMA, 374 completed 406 received 100/62.5/25 mcg ICS/LABA+LAMA, 383 completed 407 received 100/25 mcg ICS/LABA, 374 completed 406 received 200/25 mcg ICS/LABA, 378 completed 404 received 200/31.25/25 mcg ICS/LABA+LAMA (not included in this review) 408 received 200/62.5/25 mcg ICS/LABA+LAMA (not included in this review)
Duration of follow-up	52 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular moderate dose ICS/LABA plus LAMA (N = 811)
100/31.25/25 or 100/62.5/25 mcg fluticasone furoate/umeclidinium/vilanterol once per day *Two study arms containing different doses combined*

Regular moderate/high dose ICS/LABA (N = 813)
100/25 or 200/25 mcg fluticasone furoate/vilanterol once per day *Two study arms containing different doses combined*

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA plus LAMA (N = 811)	Regular moderate/high dose ICS/LABA (N = 813)
% Female Sample size	n = 512 ; % = 63	n = 504 ; % = 62
Mean age (SD) Mean (SD)	52.3 (13.3)	53.6 (13.2)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Proportion receiving moderate-dose ICS Sample size	n = 549 ; % = 68	n = 531 ; % = 65

Characteristic	Regular moderate dose ICS/LABA plus LAMA (N = 811)	Regular moderate/high dose ICS/LABA (N = 813)
Asthma control ACQ-7 Mean (SD)	2.79 (0.61)	2.79 (0.61)
Lung function (% of predicted) FEV1 Mean (SD)	58.78 (12.24)	58.45 (13.12)

Outcomes

Study timepoints

- Baseline
- 24 week

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA plus LAMA, Baseline, N = 811	Regular moderate dose ICS/LABA plus LAMA, 24 week, N = 811	Regular moderate/high dose ICS/LABA, Baseline, N = 813	Regular moderate/high dose ICS/LABA, 24 week, N = 813
Mortality Final values No of events	n = NA ; % = NA	n = 2 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 471 ; % = 58	n = NA ; % = NA	n = 468 ; % = 58

Outcome	Regular moderate dose ICS/LABA plus LAMA, Baseline, N = 811	Regular moderate dose ICS/LABA plus LAMA, 24 week, N = 811	Regular moderate/high dose ICS/LABA, Baseline, N = 813	Regular moderate/high dose ICS/LABA, 24 week, N = 813
Pneumonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 27 ; % = 3	n = NA ; % = NA	n = 18 ; % = 2

Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Pneumonia (respiratory tract infections) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
DichotomousOutcomes-Mortality-NoOfEvents-Regular low-moderate dose ICS/LABA plus LAMA-Regular moderate-high dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular low-moderate dose ICS/LABA plus LAMA-Regular moderate-high dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No adherence monitoring included)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia(respiratorytractinfections)-NoOfEvents-Regular moderate dose ICS/LABA plus LAMA-Regular moderate/high dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

Lin, 2015

Bibliographic Reference	Lin, Jiangtao; Kang, Jian; Lee, Sang Haak; Wang, Changzheng; Zhou, Xiangdong; Crawford, Jodie; Jacques, Loretta; Stone, Sally; Fluticasone furoate/vilanterol 200/25 mcg in Asian asthma patients: a randomized trial.; Respiratory medicine; 2015; vol. 109 (no. 1); 44-53

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01498653
Study type	Randomised controlled trial (RCT)
Study location	Multinational - China, South Korea and the Philippines
Study setting	No additional information
Study dates	January 2012 - February 2013
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	≥12 years of age Diagnosed with asthma for at least 12 weeks

	FEV1 40-90% of predicted and ≥12% and 200 mL reversibility after receiving SABA Receiving ICS or ICS/LABA for ≥12 weeks and at a stable strength for ≥4 weeks (500 mcg FP or 250/50 FP/SAL)
Exclusion criteria	Current smokers and those with a history >10 pack years Life threatening asthma in the past 10 years Respiratory conditions that hadn't been resolved within a month Exacerbation requiring oral corticosteroids within 12 weeks Concurrent respiratory illness or any other uncontrolled disease
Recruitment / selection of participants	Recruited from 24 centres, method not reported
Intervention(s)	Following a 2-week run-in period, participants allocated to the ICS/LABA arm received 200/25 mcg fluticasone furoate/vilanterol once daily, administered in the evening via an ELLIPTA dry powder inhaler
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported

Comparator	Following a 2-week run-in period, participants allocated to the ICS arm received 500 mcg fluticasone propionate twice daily, delivered via a DISKUS inhaler
Number of participants	309 randomised 155 allocated to ICS/LABA, 136 completed 154 allocated to ICS, 119 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT and per protocol

Study arms

Regular high dose ICS/LABA (N = 155)

200/25 mcg fluticasone furoate/vilanterol once daily

Regular high dose ICS (N = 154)

500 mcg fluticasone propionate twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular high dose ICS/LABA (N = 155)	Regular high dose ICS (N = 154)
% Female Sample size	n = 96 ; % = 62	n = 86 ; % = 56
Mean age (SD)	46.9 (12.9)	48.8 (13.4)

Characteristic	Regular high dose ICS/LABA (N = 155)	Regular high dose ICS (N = 154)
Mean (SD)		
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR
Lung function Mean (SD)	63.84 (12.94)	63.07 (12.47)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular high dose ICS/LABA, Baseline, N = 155	Regular high dose ICS/LABA, 12 week, N = 155	Regular high dose ICS, Baseline, N = 154	Regular high dose ICS, 12 week, N = 154
Asthma Control (Asthma Control Test) Change scores, scale range: 5-25 Mean (SD)	NA (NA)	4.7 (3.6)	NA (NA)	4.3 (3.8)
Quality of life (Asthma Quality of Life Questionnaire) Change scores, scale range: 1-7, ICS/LABA n=140, ICS n=123 Mean (SD)	NA (NA)	0.8 (0.86)	NA (NA)	0.69 (0.92)
Reliever medication use (SABA-free days) (%) Change scores, ICS n=152 Mean (SD)	NA (NA)	32.4 (36.7)	NA (NA)	31.5 (37)
Lung function (PEF) (Litres per minute) Change scores, ICS/LABA n=154, ICS n=152 Mean (SD)	NA (NA)	46.2 (38.2)	NA (NA)	14 (38.5)

Asthma Control (Asthma Control Test) - Polarity - Higher values are better
Quality of life (Asthma Quality of Life Questionnaire) - Polarity - Higher values are better
Reliever medication use (SABA-free days) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular high dose ICS/LABA, Baseline, N = 155	Regular high dose ICS/LABA, 12 week, N = 155	Regular high dose ICS, Baseline, N = 154	Regular high dose ICS, 12 week, N = 154
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 1 ; % = 1	n = NA ; % = NA	n = 3 ; % = 2
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Pneumonia Final values No of events	n = NA ; % = NA	n = 2 ; % = 1	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 38 ; % = 25	n = NA ; % = NA	n = 41 ; % = 27

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Pneumonia - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-AsthmaControl(AsthmaControlTest)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(27% dropout rate, 20% difference in attrition between study arms, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Qualityoflife(AsthmaQualityofLifeQuestionnaire)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(27% dropout rate, 20% difference in attrition between study arms, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Relievermedicationuse(SABA-freedays)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(27% dropout rate, 20% difference in attrition between study arms, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(PEF)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(27% dropout rate, 20% difference in attrition between study arms, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(27% dropout rate, 20% difference in attrition between study arms, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(27% dropout rate, 20% difference in attrition between study arms, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(27% dropout rate, 20% difference in attrition between study arms, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(27% dropout rate, 20% difference in attrition between study arms, and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Lin, 2019

Bibliographic Reference	Lin, Jiangtao; Wan, Huanying; Kang, Jian; Ma, Qianli; Chen, Ping; Jin, Meiling; Wang, Haoyan; Liu, Shuang; Hao, Qinglin; Lin, Yong; Su, Lin; Hu, Na; Add-on Tiotropium in Chinese Patients With Moderate Asthma: A Pooled Subgroup Analysis of MezzoTinA-Asthma 1 and 2.; Allergy, asthma & immunology research; 2019; vol. 11 (no. 4); 519-528

Study details

Secondary publication of another included study- see primary study for details	Secondary publication of Kerstjens 2015: Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. The Lancet. Respiratory medicine; 2015; vol. 3 (no. 5); 367-76
Other publications associated with this study included in review	Kerstjens 2015: Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. The Lancet. Respiratory medicine; 2015; vol. 3 (no. 5); 367-76

Study arms

Regular moderate dose ICS/LABA (N = 110)
Usual ICS therapy plus 50 mcg salmeterol twice per day

Regular moderate dose ICS plus LAMA (N = 215)
Usual ICS therapy plus either 2.5 or 5 mcg tiotropium once per day *Study contained two arms containing 2.5 and 5 mcg per day, combined for this review*

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 110)	Regular moderate dose ICS plus LAMA (N = 215)
% Female Sample size	n = 57 ; % = 52	n = 125 ; % = 58
Mean age (SD) Mean (SD)	44.4 (11.5)	46.2 (12.3)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Budesonide equivalent Mean (SD)	595.3 (194.7)	589.1 (198.1)
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	70.5 (7.6)	70.3 (7.5)

Outcomes

Study timepoints

- Baseline
- 24 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 110	Regular moderate dose ICS/LABA, 24 week, N = 107	Regular moderate dose ICS plus LAMA, Baseline, N = 215	Regular moderate dose ICS plus LAMA, 24 week, N = 207
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.24 (0.29)	NA (NA)	0.2 (0.28)

Lung Function (FEV1) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 110	Regular moderate dose ICS/LABA, 24 week, N = 110	Regular moderate dose ICS plus LAMA, Baseline, N = 215	Regular moderate dose ICS plus LAMA, 24 week, N = 215
Hospital admissions Final values No of events	n = 0 ; % = 0	n = 1 ; % = 1	n = 0 ; % = 0	n = 5 ; % = 2
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Hospital admissions - Polarity - Lower values are better
Mortality - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular low-moderate dose ICS plus LAMA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Hospitaladmissions-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular low-moderate dose ICS plus LAMA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular low-moderate dose ICS plus LAMA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

Mitchell, 2003

Bibliographic Reference	Mitchell, C; Jenkins, C; Scicchitano, R; Rubinfeld, A; Kottakis, J; Formoterol (Foradil) and medium-high doses of inhaled corticosteroids are more effective than high doses of corticosteroids in moderate-to-severe asthma.; Pulmonary pharmacology & therapeutics; 2003; vol. 16 (no. 5); 299-306

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	No additional information
Study dates	No additional information
Sources of funding	Sponsored by Novartis Pharmaceutical Australia Pty Ltd
Inclusion criteria	Aged ≥18 years Moderate-severe asthma

	FEV1 ≥50% of predicted, and increased by >15% after receiving SABA Received ICS at a dose of 1000 mcg beclomethasone, or 800 mcg budesonide for at least one month before screening Waking ≥1 time per night due to asthma, asthma interfering with daily activities ≥1 time per day, using SABA ≥4 times per day or diurnal PEFv >15% on ≥2 days out of the last 7 of the run-in period
Exclusion criteria	Undergone any change in ICS dose in the previous month Used LABA or received oral corticosteroids in the previous month
Recruitment / selection of participants	Recruited from 16 centres, method not reported
Intervention(s)	Following a 2-4 week run-in period where participants received 500 mcg beclomethasone dipropionate twice daily, those randomised to the ICS/LABA arm received 250 mcg beclomethasone, two inhalations twice daily plus two inhalations of placebo, plus 12 mcg formoterol, twice daily
Population subgroups	<u>Exacerbations</u> Not reported <u>Atopy</u> Not reported
Comparator	Following a 2-4 week run-in period where participants received 500 mcg beclomethasone dipropionate twice daily, those randomised to the ICS monotherapy arm received 250 mcg beclomethasone, four inhalations twice per day, plus placebo inhalation twice per day
Number of participants	203 randomised

	102 received ICS/LABA, 95 completed 101 received ICS monotherapy, 89 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat

Study arms

Regular high dose ICS/LABA (N = 100)

250 mcg beclomethasone dipropionate, two inhalations twice daily, plus 12 mcg formoterol twice daily

Regular high dose ICS (N = 101)

250 mcg beclomethasone dipropionate, four inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular high dose ICS/LABA (N = 100)	Regular high dose ICS (N = 101)
% Female Sample size	n = 56 ; % = 55	n = 57 ; % = 54
Mean age (SD) Mean (SD)	43.9 (14.9)	43.9 (15.4)
Ethnicity Nominal	NR	NR

Characteristic	Regular high dose ICS/LABA (N = 100)	Regular high dose ICS (N = 101)
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Average daytime SABA inhalations over last 7 days of run-in Mean (SD)	3.2 (2.3)	3.3 (2.7)
Lung function (% of predicted) FEV1 Mean (SD)	71.8 (11.6)	72.4 (11.1)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular high dose ICS/LABA, Baseline, N = 100	Regular high dose ICS/LABA, 12 week, N = 100	Regular high dose ICS, Baseline, N = 101	Regular high dose ICS, 12 week, N = 101
Lung function (PEF) (Litres per minute) Final values	352.2 (119.8)	390.9 (126.5)	349.7 (103)	360.7 (107.5)

Outcome	Regular high dose ICS/LABA, Baseline, N = 100	Regular high dose ICS/LABA, 12 week, N = 100	Regular high dose ICS, Baseline, N = 101	Regular high dose ICS, 12 week, N = 101
Mean (SD)				
Reliever/rescue medication use (daytime average over study period) (Inhalations per day) Final values Mean (SD)	3.2 (2.33)	0.93 (1.38)	3.32 (2.66)	2.43 (2.43)
Reliever/rescue medication use (nighttime average over study period) (Inhalations per day) Final values Mean (SD)	1.98 (1.71)	0.69 (1.27)	1.7 (1.33)	1.43 (1.56)
Adrenal insufficiency (cortisol/creatinine ratio) (nmol/mmol) Change scores Mean (SD)	NA (NA)	3.48 (38.2)	NA (NA)	-13.38 (29.91)

Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use (daytime average over study period) - Polarity - Lower values are better
Reliever/rescue medication use (nighttime average over study period) - Polarity - Lower values are better
Adrenal insufficiency (cortisol/creatinine ratio) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Regular high dose ICS/LABA, Baseline, N = 102	Regular high dose ICS/LABA, 12 week, N = 102	Regular high dose ICS, Baseline, N = 101	Regular high dose ICS, 12 week, N = 101
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 9 ; % = 9	n = NA ; % = NA	n = 12 ; % = 12
Adverse events Final values No of events	n = NA ; % = NA	n = 69 ; % = 68	n = NA ; % = NA	n = 71 ; % = 70

Severe asthma exacerbations - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Lungfunction(PEFaverageinlast7days)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and no adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliever/rescuemedicationuse(daytimeaverageoverstudyperiod)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and no adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliever/rescuemedicationuse(nighttimeaverageoverstudyperiod)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and no adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Adrenalinsufficiency(cortisol/creatinineratio)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and no adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and no adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and no adherence monitoring included)*
Overall bias and Directness	Overall Directness	Directly applicable

Nabil, 2014

Bibliographic Reference	Nabil, NM; Elessawy, AF; Hosny, KM; Ramadan, SM; The effect of adding long acting beta 2 agonists to inhaled corticosteroids versus increasing dose of inhaled corticosteroids in improving asthma control; Egyptian journal of chest diseases and tuberculosis; 2014; vol. 63 (no. 4); 761-764

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Egypt
Study setting	Outpatient chest clinic
Study dates	January 2010 - December 2012
Sources of funding	No additional information
Inclusion criteria	Aged ≥18 years Moderate-severe persistent asthma

	Uncontrolled on low dose ICS (budesonide or beclomethasone at 400 mcg per day)
Exclusion criteria	People using systemic corticosteroids Had a respiratory infection affecting asthma control within 4 weeks Severe cardio-pulmonary disease or other concomitant disease Smokers
Recruitment / selection of participants	Recruited from the outpatient chest clinic of a university hospital, method not reported
Intervention(s)	Participants received 400/12 mcg budesonide/formoterol twice daily
Population subgroups	Exacerbations Not reported Atopy Not reported
Comparator	Participants received 800 mcg budesonide twice daily
Number of participants	60 randomised 30 received ICS/LABA 30 received ICS monotherapy

Duration of follow-up	6 months
Indirectness	Downgraded by one increment due to population indirectness - no description of what defined uncontrolled asthma
Additional comments	Unclear

Study arms

Regular moderate dose ICS/LABA (N = 30)
400/12 mcg budesonide/formoterol, twice daily

Regular high dose ICS (N = 30)
800 mcg budesonide, twice daily

Characteristics

Study-level characteristics

Characteristic	Study (N = 60)
% Female Nominal	NR
Mean age (SD) Range	20 to 60
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Characteristic	Study (N = 60)
ICS dose Nominal	400
Asthma control Nominal	NR

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 30)	Regular high dose ICS (N = 30)
Lung function (Unclear units) FEV1 Mean (SD)	55.8 (3.1)	58.4 (6.8)

Outcomes

Study timepoints

- Baseline
- 6 month

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 30	Regular moderate dose ICS/LABA, 6 month, N = 30	Regular high dose ICS, Baseline, N = 30	Regular high dose ICS, 6 month, N = 30
Lung Function (FEV1) (% predicted) Final values	55.8 (3.1)	65.7 (4.8)	58.4 (6.8)	62 (4.5)

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 30	Regular moderate dose ICS/LABA, 6 month, N = 30	Regular high dose ICS, Baseline, N = 30	Regular high dose ICS, 6 month, N = 30
Mean (SD)				

Lung Function (FEV1) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, unblinded trial with no information on switching between groups or co-interventions and no adherence not reported)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(downgraded for indirectness of population (uncontrolled asthma not defined))*

Noonan, 2006

Bibliographic Reference	Noonan, Michael; Rosenwasser, Lanny J; Martin, Paula; O'Brien, Christopher D; O'Dowd, Liza; Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomised clinical trial.; Drugs; 2006; vol. 66 (no. 17); 2235-54

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	AstraZeneca LP SD-039-0717
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Tertiary care - respiratory or allergy specialty clinical practice
Study dates	July 2002 - January 2004
Sources of funding	Funded by AstraZeneca
Inclusion criteria	≥12 years of age Asthma diagnosis for ≥6 months

	Receiving moderate-high dose ICS, either alone or in combination with other asthma maintenance medications consistently for ≥4 weeks FEV1 45-85% of predicted FEV1 reversibility ≥12% and ≥0.20 L after receiving SABA
Exclusion criteria	Hospitalisation or emergency treatment for asthma ≥1 time in the past 6 months Requiring systemic corticosteroids within the past month >10 pack year smoking history
Recruitment / selection of participants	Recruited from 84 centres, method not reported
Intervention(s)	Following a two-week run-in period where participants received 80 mcg budesonide, two inhalations twice daily plus salbutamol as-needed for symptom relief, those randomised to the ICS/LABA arm received 160/4.5 mcg budesonide/formoterol, two inhalations twice daily. Those randomised to the ICS plus LABA arm received 160 mcg budesonide plus 4.5 mcg formoterol, two inhalations twice daily from separate inhalers. *Combination and concurrent ICS/LABA therapy arms combined for this review*
Population subgroups	Exacerbations Not reported

	Atopy Not reported
Comparator	Following a two-week run-in period where participants received 80 mcg budesonide, two inhalations twice daily plus salbutamol as-needed for symptom relief, those randomised to the ICS arm received 160 mcg budesonide, two inhalations twice daily. *Study also included an additional two arms containing formoterol alone or placebo. These are not relevant to this review and have not been included in this analysis*
Number of participants	596 randomised (248 excluded from this review due to receiving placebo or formoterol alone) 239 received ICS/LABA (124 ICS/LABA, 115 ICS+LABA), 183 completed 109 received ICS monotherapy, 78 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat

Study arms

Regular moderate dose ICS/LABA (N = 239)

160/4.5 mcg budesonide/formoterol, two inhalations twice daily, in a combination inhaler or administered concurrently in separate inhalers *Two study arms combined that administered drugs in combination and concurrently for this review*

Regular moderate dose ICS (N = 109)
160 mcg budesonide, two inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 239)	Regular moderate dose ICS (N = 109)
% Female Sample size	n = 145 ; % = 61	n = 71 ; % = 65
Mean age (SD) Mean (SD)	41.1 (15.1)	40.7 (14.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 187 ; % = 78	n = 84 ; % = 77
Black Sample size	n = 38 ; % = 16	n = 17 ; % = 16
Other Sample size	n = 14 ; % = 6	n = 8 ; % = 7
Comorbidities Nominal	NR	NR

Characteristic	Regular moderate dose ICS/LABA (N = 239)	Regular moderate dose ICS (N = 109)
ICS dose Mean (SD)	578.6 (234.8)	589.7 (252.4)
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	66.7 (10.4)	68.7 (10.7)

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 239	Regular moderate dose ICS/LABA, 12 week, N = 239	Regular moderate dose ICS, Baseline, N = 109	Regular moderate dose ICS, 12 week, N = 109
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 13 ; % = 5	n = NA ; % = NA	n = 5 ; % = 5

Severe asthma exacerbations - Polarity - Lower values are better
Severe asthma exacerbation defined as requiring emergency treatment, hospitalisation or use of an asthma medication not allowed by the protocol (other ICSs, LABAs, leukotriene antagonists, nebulised salbutamol, systemic corticosteroids)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored, 25% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

O'Byrne, 2005

Bibliographic Reference	O'Byrne, Paul M; Bisgaard, Hans; Godard, Philippe P; Pistolesi, Massimo; Palmqvist, Mona; Zhu, Yuanjue; Ekstrom, Tommy; Bateman, Eric D; Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma.; American journal of respiratory and critical care medicine; 2005; vol. 171 (no. 2); 129-36

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by AstraZeneca
Inclusion criteria	Aged 4-80 years Asthma treated with 400-1000 mcg (adults) or 200-500 mcg (children 4-11 years) per day at a constant dose for ≥3 months

	At least one exacerbation in the past year FEV1 60-100% of predicted with ≥12% reversibility ≥12 inhalations (≥8 for children) of as-needed medication during the last 10 days of the run-in
Exclusion criteria	>10 inhalations (>7 for children) of as-needed medication on any day of the run-in Exacerbation during the run-in
Recruitment / selection of participants	Recruited from 246 centres, method not reported
Intervention(s)	Following the run-in period, participants allocated to the regular ICS/LABA plus ICS/LABA as-needed arm received 80/4.5 budesonide/formoterol, twice daily plus additional inhalations as-needed for symptom relief. Children were given half the maintenance dose once daily in the evening. Adults could use a maximum of 10 as-needed inhalations per day, and children 7. All treatments were administered by Turbuhaler.
Population subgroups	**Exacerbations** Yes - inclusion criteria was at least one exacerbation in the past year **Atopy** Not reported

Comparator	Following the run-in period, participants allocated to the regular ICS arm received 320 mcg budesonide twice daily, plus 0.4 mg terbutaline as-needed for symptom relief. Children were given half the maintenance dose once daily in the evening. Adults could use a maximum of 10 as-needed inhalations per day, and children 7. *Study also contained an arm where participants received 80/4.5 mcg budesonide/formoterol twice daily plus 0.4 mg terbutaline as-needed - excluded from this review, but included in 3.2a, due to not containing a relevant intervention (low-dose ICS/LABA, protocol specified moderate-high dose)*
Number of participants	2760 randomised 925 allocated to ICS/LABA + ICS/LABA as-needed 926 allocated to ICS 909 allocated to ICS/LABA + SABA as-needed (excluded from this review)
Duration of follow-up	12 months
Indirectness	Downgraded by one increment due to population indirectness - included both adults and children (12%)
Additional comments	ITT

Study arms

Regular moderate dose ICS (N = 926)

320 mcg budesonide twice daily plus terbutaline as-needed for symptom relief

Low dose ICS/formoterol MART (N = 925)

80/4.5 mcg budesonide/formoterol twice daily plus additional inhalations as-needed for symptom relief

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS (N = 926)	Low dose ICS/formoterol MART (N = 925)
% Female Sample size	n = 510 ; % = 55	n = 504 ; % = 54
Mean age (SD) Proportion aged 4-11 years Nominal	36	35
Mean age (SD) Proportion aged 4-11 years Range	4 to 79	4 to 77
Mean age (SD) Proportion aged 4-11 years Sample size	n = 106 ; % = 11	n = 108 ; % = 13
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Proportion receiving LABAs Nominal	620	619

Characteristic	Regular moderate dose ICS (N = 926)	Low dose ICS/formoterol MART (N = 925)
ICS dose Proportion receiving LABAs Range	100 to 1000	200 to 1200
ICS dose Proportion receiving LABAs Sample size	n = 256 ; % = 28	n = 250 ; % = 27
Asthma control Reliever medication use Nominal	NA	NA
Asthma control Reliever medication use Range	NA to NA	NA to NA
Daytime Nominal	1.69	1.74
Daytime Range	0 to 7	0 to 8
Nighttime Nominal	0.72	0.72
Nighttime Range	0 to 3.7	0 to 5.7

Characteristic	Regular moderate dose ICS (N = 926)	Low dose ICS/formoterol MART (N = 925)
Lung function (% of predicted) FEV1 Nominal	73	73
Lung function (% of predicted) FEV1 Range	49 to 100	43 to 108

Outcomes

Study timepoints

- Baseline
- 52 week

Dichotomous Outcomes

Outcome	Regular moderate dose ICS, Baseline, N = 925	Regular moderate dose ICS, 52 week, N = NR	Low dose ICS/formoterol MART, Baseline, N = 922	Low dose ICS/formoterol MART, 52 week, N = NR
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 176 ; % = 19	n = NA ; % = NA	n = 101 ; % = 11
Pneumonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 182 ; % = 20	n = NA ; % = NA	n = 158 ; % = 17

Outcome	Regular moderate dose ICS, Baseline, N = 925	Regular moderate dose ICS, 52 week, N = NR	Low dose ICS/formoterol MART, Baseline, N = 922	Low dose ICS/formoterol MART, 52 week, N = NR
Adverse events Final values No of events	n = NA ; % = NA	n = 528 ; % = 57	n = NA ; % = NA	n = 496 ; % = 54

Severe asthma exacerbations - Polarity - Lower values are better
Pneumonia (respiratory tract infections) - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Contrast Outcomes

Outcome	Low dose ICS/formoterol MART vs Regular moderate dose ICS, Baseline, N2 = 926, N1 = 925	Low dose ICS/formoterol MART vs Regular moderate dose ICS, 52 week, N2 = 926, N1 = 925
Reliever/rescue medication use (daytime SABA use) (Puffs per day) Final values Mean (p value)	NR (NR)	-0.3 (<0.001)
Reliever/rescue medication use (night time SABA use) (Puffs per night) Final values Mean (p value)	NR (NR)	-0.15 (<0.001)
Lung Function (FEV1) (Litres) Change scores Mean (p value)	NA (NA)	0.1 (<0.001)
Lung function (PEF) (Litres per minute) Change scores	NA (NA)	16 (<0.001)

Outcome	Low dose ICS/formoterol MART vs Regular moderate dose ICS, Baseline, N2 = 926, N1 = 925	Low dose ICS/formoterol MART vs Regular moderate dose ICS, 52 week, N2 = 926, N1 = 925
Mean (p value)		

Reliever/rescue medication use (daytime SABA use) - Polarity - Lower values are better
Reliever/rescue medication use (night time SABA use) - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS-Regular ICS/LABA plus ICS/LABA as-needed-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 85% adherence to maintenance medication and attrition rates not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia(respiratorytractinfections)-NoOfEvents-Regular moderate-high dose ICS-Regular ICS/LABA plus ICS/LABA as-needed-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 85% adherence to maintenance medication and attrition rates not reported)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS-Regular ICS/LABA plus ICS/LABA as-needed-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 85% adherence to maintenance medication and attrition rates not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Reliever/rescuemedicationuse(daytimeSABAuse)-MeanPValue-Regular moderate-high dose ICS-Regular ICS/LABA plus ICS/LABA as-needed-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 85% adherence to maintenance medication and attrition rates not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Reliever/rescuemedicationuse(nighttimeSABAuse)-MeanPValue-Regular moderate-high dose ICS-Regular ICS/LABA plus ICS/LABA as-needed-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 85% adherence to maintenance medication and attrition rates not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-LungFunction(FEV1)-MeanPValue-Regular moderate-high dose ICS-Regular ICS/LABA plus ICS/LABA as-needed-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 85% adherence to maintenance medication and attrition rates not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Lungfunction(PEF)-MeanPValue-Regular moderate-high dose ICS-Regular ICS/LABA plus ICS/LABA as-needed-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 85% adherence to maintenance medication and attrition rates not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

O'Byrne, 2014

Bibliographic Reference	O'Byrne, Paul M; Bleecker, Eugene R; Bateman, Eric D; Busse, William W; Woodcock, Ashley; Forth, Richard; Toler, William T; Jacques, Loretta; Lotvall, Jan; Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma.; The European respiratory journal; 2014; vol. 43 (no. 3); 773-82

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01134042
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	No additional information
Study dates	June 2010 - October 2011
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	Aged ≥12 years Documented use of ICS, with or without LABA, for ≥12 weeks with stable ICS dose (FP 500 mg twice daily (or equivalent) or mid-dose ICS/LABA (FP/salmeterol 250/50 mg twice daily or equivalent)) for ≥4 weeks

	FEV1 of 40–90% of predicted normal FEV1 reversibility of ≥12% and ≥200 mL on inhalation of salbutamol Asthma symptoms equating to a score ≥3 on the asthma symptom scale and/or daily SABA use on ≥4 of the final 7 days of the run-in
Exclusion criteria	History of life-threatening asthma in the previous 10 year Asthma exacerbation requiring overnight hospitalisation or emergency department attendance within 6 months of screening Asthma exacerbation requiring oral corticosteroids within 12 weeks of screening
Recruitment / selection of participants	Recruited from 63 centres in Germany, Japan, Poland, Romania, Russia and USA, method not reported
Intervention(s)	Following a 4-week run-in period where participants were maintained on their usual dose of ICS, and LABAs were removed, those randomised to the ICS/LABA arm received 200/25 mcg fluticasone fuorate/vilanterol once daily
Population subgroups	Exacerbations Not reported Atopy Not reported

Comparator	Following a 4-week run-in period where participants were maintained on their usual dose of ICS, and LABAs were removed, those randomised to the ICS monotherapy arms received 500 mcg fluticasone propionate, twice daily, or 200 mcg fluticasone furoate once daily
Number of participants	586 randomised 197 received ICS/LABA, 169 completed 389 received ICS monotherapy, 307 completed
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	Intention to treat and per protocol

Study arms

Regular high dose ICS/LABA (N = 197)

200/25 (184/22 emitted) mcg fluticasone fuorate/vilanterol, once daily

Regular high dose ICS (N = 389)

500 mcg fluticasone propionate, twice daily, or 200 mcg fluticasone furoate once daily *Two study arms combined for this review*

Characteristics

Arm-level characteristics

Characteristic	Regular high dose ICS/LABA (N = 197)	Regular high dose ICS (N = 389)
% Female Sample size	n = 116 ; % = 59	n = 116 ; % = 59

Characteristic	Regular high dose ICS/LABA (N = 197)	Regular high dose ICS (N = 389)
Mean age (SD) Mean (SD)	46.6 (15.1)	47.3 (14.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Sample size	n = NA ; % = NA	n = NA ; % = NA
ICS monotherapy Sample size	n = 47 ; % = 24	n = 93 ; % = 24
ICS + LABA Sample size	n = 150 ; % = 76	n = 296 ; % = 76
Asthma control (%) Symptom free days Mean (SD)	5.1 (15.2)	2.7 (9.8)
Lung function (% of predicted) FEV1 Mean (SD)	66.6 (12.6)	67.2 (12.3)

Outcomes

Study timepoints

- Baseline
- 24 week

Continuous Outcomes

Outcome	Regular high dose ICS/LABA, Baseline, N = 197	Regular high dose ICS/LABA, 24 week, N = 197	Regular high dose ICS, Baseline, N = 389	Regular high dose ICS, 24 week, N = 389
Quality of Life (total asthma quality of life questionnaire) Change scores, scale range 0-7 Mean (SD)	NA (NA)	0.93 (0.91)	NA (NA)	0.89 (0.97)
Asthma Control (Asthma Control Test) Change scores, scale range 5-25 Mean (SD)	NA (NA)	5.5 (3.9)	NA (NA)	4.9 (4.1)
Lung Function (FEV1) (ml) Change scores, ICS/LABA follow-up n=187, ICS monotherapy n=376 Mean (SD)	NA (NA)	394 (413)	NA (NA)	192 (418)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	51.8 (41.3)	NA (NA)	18.5 (41.2)

Outcome	Regular high dose ICS/LABA, Baseline, N = 197	Regular high dose ICS/LABA, 24 week, N = 197	Regular high dose ICS, Baseline, N = 389	Regular high dose ICS, 24 week, N = 389
Reliever/rescue medication use (days without use) (%) Change scores Mean (SD)	NA (NA)	38.2 (34)	NA (NA)	29.3 (34.2)

Quality of Life (total asthma quality of life questionnaire) - Polarity - Higher values are better
Asthma Control (Asthma Control Test) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use (days without use) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular high dose ICS/LABA, Baseline, N = 197	Regular high dose ICS/LABA, 24 week, N = 197	Regular high dose ICS, Baseline, N = 389	Regular high dose ICS, 24 week, N = 389
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 8 ; % = 2
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 85 ; % = 43	n = NA ; % = NA	n = 173 ; % = 44

Outcome	Regular high dose ICS/LABA, Baseline, N = 197	Regular high dose ICS/LABA, 24 week, N = 197	Regular high dose ICS, Baseline, N = 389	Regular high dose ICS, 24 week, N = 389
Pneumonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 7 ; % = 4	n = NA ; % = NA	n = 14 ; % = 4

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Pneumonia (respiratory tract infections) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-QualityofLife(totalasthmaqualityoflifequestionnaire)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not reported, 19% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-AsthmaControl(AsthmaControlTest)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not reported, 19% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not reported, 19% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(morningPEF)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not reported, 19% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliever/rescuemedicationuse(dayswithoutuse)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not reported, 19% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not reported, 19% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not reported, 19% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not reported, 19% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia(respiratorytractinfections)-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not reported, 19% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Indirectly applicable

Paggiaro, 2016

Bibliographic Reference	Paggiaro, Pierluigi; Corradi, Massimo; Latorre, Manuela; Raptis, Helene; Muraro, Annamaria; Gessner, Christian; Siergiejko, Zenon; Scuri, Mario; Petruzzelli, Stefano; High strength extrafine pMDI beclometasone/formoterol (200/6 mug) is effective in asthma patients not adequately controlled on moderate-high dose of inhaled corticosteroids.; BMC pulmonary medicine; 2016; vol. 16 (no. 1); 180

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT01577082
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Chiesi Farmaceutici
Inclusion criteria	Aged ≥18 years FEV1 ≥40 and <80% of predicted normal value

	Change in FEV1 ≥12% and ≥200 mL after SABA Partly or not controlled asthma, based on GINA asthma control parameters, and an asthma control questionnaire >0.75 Receiving high dose ICS monotherapy (BDP non-extrafine >1000 µg/day, or equivalent) or moderate dose of ICS (BDP non-extrafine 500–1000 µg/day or equivalent) in combination with LABA Patients were eligible for randomisation if their asthma was still not fully controlled at the end of a 2-week run-in period
Exclusion criteria	Deteriorating asthma resulting in a change of asthma therapy in the 4 weeks before screening
Recruitment / selection of participants	Recruited from sites in Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Poland, Russia and the UK
Intervention(s)	Participants randomised to the ICS/LABA arm received 200/6 mcg beclomethasone dipropionate/formoterol fuorate, two inhalations twice daily
Population subgroups	Exacerbations Not reported Atopy Not reported
Comparator	Participants randomised to the ICS monotherapy arm received 100 mcg beclomethasone dipropionate, four inhalations twice per day
Number of participants	376 randomised 184 received ICS/LABA, 178 completed 175 received ICS monotherapy, 164 completed

Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat

Study arms

Regular moderate dose ICS/LABA (N = 184)

200/6 mcg beclomethasone dipropionate/formoterol fuorate, two inhalations twice daily

Regular moderate dose ICS (N = 175)

100 mcg beclomethasone dipropionate, four inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 184)	Regular moderate dose ICS (N = 175)
% Female Sample size	n = 100 ; % = 54.3	n = 112 ; % = 64
Mean age (SD) Mean (SD)	49.5 (13.7)	49.1 (14.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Characteristic	Regular moderate dose ICS/LABA (N = 184)	Regular moderate dose ICS (N = 175)
ICS dose Nominal	NR	NR
Asthma control ACQ Mean (SD)	2.12 (0.6)	2.12 (0.6)
Lung function (% of predicted) FEV1 Mean (SD)	64.7 (8.1)	64.3 (9.5)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 192	Regular moderate dose ICS/LABA, 12 week, N = 184	Regular moderate dose ICS, Baseline, N = 184	Regular moderate dose ICS, 12 week, N = 175
Lung function (PEF) (Litres per minute) Change scores, ICS/LABA n=182, ICS n=170 Mean (SD)	NA (NA)	18 (42)	NA (NA)	-1 (40)
Adrenal insufficiency (serum cortisol) 0-24h AUC, change scores, number of	NA (NA)	1 (0.4)	NA (NA)	0.8 (0.3)

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 192	Regular moderate dose ICS/LABA, 12 week, N = 184	Regular moderate dose ICS, Baseline, N = 184	Regular moderate dose ICS, 12 week, N = 175
participants unclear - paper states 15% of randomised participants had cortisol assessed Mean (SD)				
Severe exacerbation rate Final values, total number of events Nominal	NA	4	NA	7

Lung function (PEF) - Polarity - Higher values are better
Adrenal insufficiency (serum cortisol) - Polarity - Higher values are better
Severe exacerbation rate - Polarity - Lower values are better
Unclear what duration PEF was monitored over, serum cortisol measured in 15% of participants

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 189	Regular moderate dose ICS/LABA, 12 week, N = 189	Regular moderate dose ICS, Baseline, N = 180	Regular moderate dose ICS, 12 week, N = 180
Severe asthma exacerbations Number of participants with at least one event No of events	n = NA ; % = NA	n = 4 ; % = 2	n = NA ; % = NA	n = 6 ; % = 3
Adverse events Final values No of events	n = NA ; % = NA	n = 29 ; % = 15	n = NA ; % = NA	n = 30 ; % = 17

Severe asthma exacerbations - Polarity - Lower values are better

Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Lungfunction(morningPEF)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and unclear what duration PEF was assessed over)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Adrenalinsufficiency(serumcortisol)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and No information on dropout rate from 15% subset of participants who had cortisol measured)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Severeexacerbationrate-Nominal-Regular moderate dose ICS/LABA-Regular moderate dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Patel, 2013

Bibliographic Reference	Patel, Mitesh; Pilcher, Janine; Pritchard, Alison; Perrin, Kyle; Travers, Justin; Shaw, Dominick; Holt, Shaun; Harwood, Matire; Black, Peter; Weatherall, Mark; Beasley, Richard; Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial.; The Lancet. Respiratory medicine; 2013; vol. 1 (no. 1); 32-42

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	ACTRN12610000515099
Study type	Randomised controlled trial (RCT)
Study location	New Zealand
Study setting	Four primary healthcare practices and one hospital
Study dates	June 2010 - September 2011
Sources of funding	Funded by the Health Research Council of New Zealand
Inclusion criteria	Aged 16-65 years Physician diagnosis of asthma

	Receiving ICS At least one exacerbation requiring a GP/ER visit resulting in oral corticosteroid prescription in the past year
Exclusion criteria	Diagnosis of COPD Onset of respiratory symptoms after the age of 40 in current or ex-smokers Smoking history >10 pack years
Recruitment / selection of participants	Recruited from 5 centres, method not reported
Intervention(s)	Participants allocated to the regular ICS/LABA plus as-needed ICS/LABA received 200/6 mcg budesonide/formoterol, two inhalations twice daily, with additional inhalations as-needed for symptom relief, all administered by Symbicort Turbuhaler
Population subgroups	**Exacerbations** Yes. At least one exacerbation requiring a GP/ER visit resulting in oral corticosteroid prescription in the past year **Atopy** Not reported
Comparator	Participants allocated to the ICS/LABA arm received 200/6 mcg budesonide/formoterol, two inhalations twice daily administered by Symbicort Turbuhaler, plus 100 or 200 mcg salbutamol as-needed for symptom relief administered by Ventolin inhaler
Number of participants	303 randomised

	151 allocated to ICS/LABA + ICS/LABA as-needed, 134 completed 152 allocated to ICS/LABA + SABA as-needed, 141 completed
Duration of follow-up	24 weeks
Indirectness	Downgraded by one increment due to population indirectness - 15% of participants did not have asthma that was uncontrolled
Additional comments	Unclear

Study arms

Moderate dose ICS/formoterol MART (N = 151)

200/6 mcg budesonide/formoterol, two inhalations twice daily plus additional inhalations as-needed for symptom relief

Regular moderate dose ICS/LABA (N = 152)

200/6 mcg budesonide/formoterol, two inhalations twice daily plus salbutamol as-needed for symptom relief

Characteristics

Arm-level characteristics

Characteristic	Moderate dose ICS/formoterol MART (N = 151)	Regular moderate dose ICS/LABA (N = 152)
% Female Sample size	n = 103 ; % = 68	n = 106 ; % = 70
Mean age (SD) Mean (SD)	41.3 (13.7)	42.6 (14.5)
Ethnicity	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Moderate dose ICS/formoterol MART (N = 151)	Regular moderate dose ICS/LABA (N = 152)
Sample size		
European Sample size	n = 113 ; % = 75	n = 118 ; % = 78
Maori Sample size	n = 25 ; % = 17	n = 19 ; % = 13
Pacific Islander Sample size	n = 5 ; % = 3	n = 10 ; % = 7
Other Sample size	n = 8 ; % = 5	n = 5 ; % = 3
Comorbidities Nominal	NR	NR
ICS dose Proportion receiving LABAs Sample size	n = 92 ; % = 61	n = 103 ; % = 68
ICS dose Proportion receiving LABAs Mean (SD)	804.5 (352.7)	812.6 (370.4)
Asthma control ACQ-7 Score Mean (SD)	1.87 (0.96)	1.9 (1.13)

Characteristic	Moderate dose ICS/formoterol MART (N = 151)	Regular moderate dose ICS/LABA (N = 152)
Lung function (% of predicted) FEV1 Mean (SD)	81.6 (18.9)	80.4 (20.5)

Outcomes

Study timepoints

- Baseline
- 24 week

Continuous Outcomes

Outcome	Moderate dose ICS/formoterol MART, Baseline, N = 151	Moderate dose ICS/formoterol MART, 24 week, N = 151	Regular moderate dose ICS/LABA, Baseline, N = 152	Regular moderate dose ICS/LABA, 24 week, N = 152
Asthma control (ACQ-7) Final values, scale range: 0-6 Mean (SD)	1.87 (0.96)	1.04 (0.76)	1.9 (1.13)	1.3 (1.08)
Lung Function (FEV1) (% of predicted) Final values Mean (SD)	81.6 (18.9)	87.1 (17)	80.4 (20.5)	84.1 (22)
Severe exacerbation rate	NA	35	NA	66

Outcome	Moderate dose ICS/formoterol MART, Baseline, N = 151	Moderate dose ICS/formoterol MART, 24 week, N = 151	Regular moderate dose ICS/LABA, Baseline, N = 152	Regular moderate dose ICS/LABA, 24 week, N = 152
Final values, total number of events Nominal				

Asthma control (ACQ-7) - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Severe exacerbation rate - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Moderate dose ICS/formoterol MART, Baseline, N = 151	Moderate dose ICS/formoterol MART, 24 week, N = 151	Regular moderate dose ICS/LABA, Baseline, N = 152	Regular moderate dose ICS/LABA, 24 week, N = 152
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 28 ; % = 19	n = NA ; % = NA	n = 50 ; % = 33
Hospital admissions Final values No of events	n = NA ; % = NA	n = 2 ; % = 1	n = NA ; % = NA	n = 2 ; % = 1
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Severe asthma exacerbations - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better

Mortality - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Asthmacontrol(ACQ-7)-MeanSD-Regular ICS/LABA plus ICS/LABA as-needed-Regular moderate-high dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unbalanced use of oral prednisolone between study arms and open-label study design with a subjective outcome measure)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular ICS/LABA plus ICS/LABA as-needed-Regular moderate-high dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unbalanced use of oral prednisolone between study arms and adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular ICS/LABA plus ICS/LABA as-needed-Regular moderate-high dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unbalanced use of oral prednisolone between study arms and adherence not monitored)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Hospitaladmissions-NoOfEvents-Regular ICS/LABA plus ICS/LABA as-needed-Regular moderate-high dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unbalanced use of oral prednisolone between study arms and adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular ICS/LABA plus ICS/LABA as-needed-Regular moderate-high dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unbalanced use of oral prednisolone between study arms and adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Severeexacerbationrate-Nominal-Moderate dose ICS/formoterol MART-Regular moderate dose ICS/LABA-t24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unbalanced use of oral prednisolone between study arms and adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Pavord, 2009

Bibliographic Reference	Pavord, Ian D; Jeffery, Peter K; Qiu, Yusheng; Zhu, Jie; Parker, Debbie; Carlsheimer, Asa; Naya, Ian; Barnes, Neil C; Airway inflammation in patients with asthma with high-fixed or low-fixed plus as-needed budesonide/formoterol.; The Journal of allergy and clinical immunology; 2009; vol. 123 (no. 5); 1083-7

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00244608
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	No additional information
Study dates	May 2005 - March 2007
Sources of funding	Supported by AstraZeneca
Inclusion criteria	Aged 18-65 years Receiving ICS at a dose of 400-1000 mcg in combination with a LABA, or 800-1600 as monotherapy

	FEV1 ≥60% of predicted and ≥12% and 200 mL reversibility Used SABA or reported symptoms on ≥4 of the last 7 days of the run-in period Morning PEF 50-85% of predicted during the last 7 days of the run-in period
Exclusion criteria	None reported
Recruitment / selection of participants	Recruited from 22 centres, method not reported
Intervention(s)	Participants allocated to the regular ICS/LABA plus ICS/LABA as-needed arm received 200/6 mcg budesonide/formoterol, one inhalation twice per day and additional inhalations as-needed for symptom relief
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Participants allocated to the regular ICS/LABA plus SABA as-needed arm received 400/12 mcg budesonide/formoterol and 400 mcg budesonide, one inhalation each twice per day, plus 0.5 mg terbutaline as-needed for symptom relief
Number of participants	127 randomised 63 allocated to ICS/LABA plus ICS/LABA as-needed, 58 completed 64 allocated to ICS/LABA plus SABA as-needed, 60 completed

Duration of follow-up	12 months
Indirectness	None
Additional comments	ITT

Study arms

Regular high dose ICS/LABA (N = 63)

400/12 mcg budesonide/formoterol plus 400 mcg budesonide, one inhalation of each twice per day, plus 500 mcg terbutaline as-needed for symptom relief

Low dose ICS/formoterol MART (N = 64)

200/6 mcg budesonide/formoterol, one inhalation twice per day, plus additional inhalations as-needed for symptom relief

Characteristics

Arm-level characteristics

Characteristic	Regular high dose ICS/LABA (N = 63)	Low dose ICS/formoterol MART (N = 64)
% Female Sample size	n = 29 ; % = 46	n = 29 ; % = 45
Mean age (SD) Nominal	41	39
Mean age (SD) Range	20 to 65	19 to 63
Ethnicity	NR	NR

Characteristic	Regular high dose ICS/LABA (N = 63)	Low dose ICS/formoterol MART (N = 64)
Nominal		
Comorbidities Nominal	NR	NR
ICS dose Proportion receiving LABAs Nominal	867	741
ICS dose Proportion receiving LABAs Range	200 to 1600	200 to 1600
ICS dose Proportion receiving LABAs Sample size	n = 51 ; % = 81	n = 54 ; % = 84
Asthma control (Puffs per day) Reliever use Nominal	1.2	1.5
Asthma control (Puffs per day) Reliever use Range	0 to 7.4	0 to 6
Lung function (% of predicted) FEV1 Nominal	80.6	81.4

Characteristic	Regular high dose ICS/LABA (N = 63)	Low dose ICS/formoterol MART (N = 64)
Lung function (% of predicted) FEV1 Range	60 to 110	58 to 121

Outcomes

Study timepoints

- Baseline
- 12 month

Dichotomous Outcomes

Outcome	Regular high dose ICS/LABA, Baseline, N = 63	Regular high dose ICS/LABA, 12 month, N = 63	Low dose ICS/formoterol MART, Baseline, N = 64	Low dose ICS/formoterol MART, 12 month, N = 64
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Mortality - Polarity - Lower values are better

Contrast Outcomes

Outcome	Low dose ICS/formoterol MART vs Regular high dose ICS/LABA, Baseline, N2 = 63, N1 = 64	Low dose ICS/formoterol MART vs Regular high dose ICS/LABA, 12 month, N2 = 63, N1 = 64
Reliever/rescue medication use (Puffs per day) Final values	NA (NA)	0.28 (0.22)

Outcome	Low dose ICS/formoterol MART vs Regular high dose ICS/LABA, Baseline, N2 = 63, N1 = 64	Low dose ICS/formoterol MART vs Regular high dose ICS/LABA, 12 month, N2 = 63, N1 = 64
Mean (p value)		
Severe exacerbation rate Final values, per person year Mean (95% CI)	NA (NA to NA)	1.02 (0.52 to 2.02)

Reliever/rescue medication use - Polarity - Lower values are better
Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular ICS/LABA plus ICS/LABA as-needed-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Reliever/rescuemedicationuse-MeanPValue-Regular moderate-high dose ICS/LABA-Regular ICS/LABA plus ICS/LABA as-needed-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Severeexacerbationrate-MeanNineFivePercentCI-Regular high dose ICS/LABA-Low dose ICS/formoterol MART-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Pertseva, 2013

Bibliographic Reference	Pertseva, Tetyana; Dissanayake, Sanjeeva; Kaiser, Kirsten; Superiority of fluticasone propionate/formoterol fumarate versus fluticasone propionate alone in patients with moderate-to-severe asthma: a randomised controlled trial.; Current medical research and opinion; 2013; vol. 29 (no. 10); 1357-69

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	ClinicalTrials.gov identifier: NCT00649025; EudraCT number: 2007-005653-37
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	Primary care and hospital clinics
Study dates	March 2008 - September 2008
Sources of funding	Funded by Skyepharma and Abbott Respiratory LLC
Inclusion criteria	≥12 years of age History of asthma for ≥12 months

	Receiving ICS at a dose of ≤500 mcg fluticasone equiv. for ≥4 weeks and be considered suitable for ICS/LABA therapy FEV1 40-80% of normal Demonstrated FEV1 reversibility after inhalation of SABA within 12 months ≥2 inhalations of SABA on ≥3 out of 7 days of the run-in ≥1 night with sleep disturbance or ≥3 days with asthma symptoms during run-in
Exclusion criteria	None reported
Recruitment / selection of participants	Recruited from 68 sites in Europe, South America and USA, method not reported
Intervention(s)	Following a run-in period where participants received 100 or 200 mcg fluticasone propionate, depending on their pre-trial ICS dose, those randomised to the ICS/LABA arm received 250/10 mcg fluticasone/salmeterol twice daily. Participants also received a placebo inhaler and a salbutamol inhaler for symptom relief.
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Following a run-in period where participants received 100 or 200 mcg fluticasone propionate, depending on their pre-trial ICS dose, those randomised to the ICS arms received 250 mcg fluticasone propionate, produced by either GlaxoSmithKline or Skyepharma, twice daily. Participants also received a placebo inhaler and a salbutamol inhaler for symptom relief.

	Two study intervention arms were combined for this review. Both provided 250 mcg fluticasone propionate twice daily with the only difference in interventions being the producer of the inhaler provided
Number of participants	438 randomised 145 received ICS/LABA, 138 completed 292 received ICS monotherapy, 253 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat with last observation carried forward

Study arms

Regular moderate dose ICS/LABA (N = 146)

250/10 mcg fluticasone/formoterol, twice daily

Regular moderate dose ICS (N = 292)

250 mcg fluticasone, twice daily *Combined two study intervention arms comparing 250 mcg fluticasone produced by GSK and SKP*

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 146)	Regular moderate dose ICS (N = 292)
% Female Sample size	n = 87 ; % = 60	n = 195 ; % = 67
Mean age (SD)	41.2 (17)	42.5 (16.7)

Characteristic	Regular moderate dose ICS/LABA (N = 146)	Regular moderate dose ICS (N = 292)
Mean (SD)		
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White/Caucasian Sample size	n = 114 ; % = 78	n = 224 ; % = 77
Black Sample size	n = 3 ; % = 2	n = 5 ; % = 2
Asian Sample size	n = 1 ; % = 1	n = 1 ; % = 1
Hispanic Sample size	n = 23 ; % = 16	n = 54 ; % = 18
Other Sample size	n = 5 ; % = 3	n = 8 ; % = 3
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR

Characteristic	Regular moderate dose ICS/LABA (N = 146)	Regular moderate dose ICS (N = 292)
Lung function (% of predicted) FEV1 Mean (SD)	63.9 (11.3)	63.3 (11.2)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 146	Regular moderate dose ICS/LABA, 12 week, N = 145	Regular moderate dose ICS, Baseline, N = 292	Regular moderate dose ICS, 12 week, N = 289
Reliever/rescue medication use (Inhalations per day) Change scores, ICS/LABA n=145, ICS n=288 Mean (SD)	NA (NA)	-1.85 (1.51)	NA (NA)	-1.5 (1.52)
Lung funtion (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.21 (0.53)	NA (NA)	0.16 (0.53)

Reliever/rescue medication use - Polarity - Lower values are better
Lung funtion (FEV1) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 146	Regular moderate dose ICS/LABA, 12 week, N = 146	Regular moderate dose ICS, Baseline, N = 292	Regular moderate dose ICS, 12 week, N = 292
Adverse events Final values No of events	n = NA ; % = NA	n = 48 ; % = 33	n = NA ; % = NA	n = 117 ; % = 40
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 1 ; % = 1	n = NA ; % = NA	n = 3 ; % = 2
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Adverse events - Polarity - Lower values are better
Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Reliever/rescuemedicationuse-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 11% dropout rate with 10% difference between dropout rates between arms and reasons for discontinuation related to participant's health status)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfuntion(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 11% dropout rate with 10% difference between dropout rates between arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 11% dropout rate with 10% difference between dropout rates between arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 11% dropout rate with 10% difference between dropout rates between arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 11% dropout rate with 10% difference between dropout rates between arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Peters, 2008

Bibliographic Reference	Peters, Stephen P; Prenner, Bruce M; Mezzanotte, William S; Martin, Paula; O'Brien, Christopher D; Long-term safety and asthma control with budesonide/formoterol versus budesonide pressurized metered-dose inhaler in asthma patients.; Allergy and asthma proceedings; 2008; vol. 29 (no. 5); 499-516

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	SD039-0728
Study type	Randomised controlled trial (RCT)
Study location	No additional information
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by AstraZeneca
Inclusion criteria	≥12 years of age Diagnosis of asthma for ≥6 months

	Receiving moderate-high dose ICS, or low-high dose ICS/LABA consistently for ≥4 weeks before screening Non-smoking with a <20 pack-year history FEV1 ≥45% of predicted ≥2 controller medication uses, ≥2 nighttime awakenings due to asthma or ≥3 rescue medication uses in the previous week FEV1 reversibility ≥12% and ≥0.20 L after receiving SABA
Exclusion criteria	Significant disease or disorder that may have impacted the study Treated with systemic corticosteroids within 30 days before screening or during the run-in period
Recruitment / selection of participants	No additional information
Intervention(s)	Following a two-week run-in period where participants received 160 mcg budesonide, two inhalations twice daily plus salbutamol as needed, those randomised to the ICS/LABA arm received 160/4.5 mcg budesonide/formoterol, two or four inhalations twice daily. Participants were also given a salbutamol inhaler for use as-needed for symptom relief. *Study had two separate arms for two and four inhalations, twice daily, of 160/4.5 mcg budesonide/formoterol, representing moderate and high doses, respectively. These study arms were combined for this review.*
Population subgroups	Exacerbations Not reported

	Atopy Not reported
Comparator	Following a two-week run-in period where participants received 160 mcg budesonide, two inhalations twice daily plus salbutamol as needed, those randomised to the ICS arm received 160 mcg budesonide, four inhalations twice daily. Participants were also given a salbutamol inhaler for use as-needed for symptom relief.
Number of participants	706 randomised 575 received ICS/LABA, 472 completed 133 received ICS monotherapy, 107 completed
Duration of follow-up	52 weeks
Indirectness	None
Additional comments	Intention to treat

Study arms

Regular moderate/high dose ICS/LABA (N = 575)
160/4.5 mcg budesonide/formoterol, two or four inhalations twice daily *2 study arms combined examining two and four inhalations for this review*

Regular high dose ICS (N = 133)
160 mcg budesonide, four inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate/high dose ICS/LABA (N = 575)	Regular high dose ICS (N = 133)
% Female Sample size	n = 357 ; % = 62	n = 91 ; % = 68
Mean age (SD) Mean (SD)	40.5 (16.5)	39.8 (15.6)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 500 ; % = 87	n = 116 ; % = 87
Black Sample size	n = 46 ; % = 8	n = 14 ; % = 11
Asian Sample size	n = 9 ; % = 2	n = 0 ; % = 0
Other Sample size	n = 20 ; % = 3	n = 3 ; % = 2
Comorbidities Nominal	NR	NR
ICS dose	504 (238)	509 (273)

Characteristic	Regular moderate/high dose ICS/LABA (N = 575)	Regular high dose ICS (N = 133)
Mean (SD)		
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	74.2 (14.3)	72.7 (13.6)

Outcomes

Study timepoints

- Baseline
- 52 week

Continuous Outcomes

Outcome	Regular moderate/high dose ICS/LABA, Baseline, N = 575	Regular moderate/high dose ICS/LABA, 52 week, N = 575	Regular high dose ICS, Baseline, N = 133	Regular high dose ICS, 52 week, N = 133
Rescue/reliever medication use (Inhalations per day) Change scores, ICS/LABA n=568, ICS n=130 Mean (SD)	NA (NA)	-0.79 (1.51)	NA (NA)	-0.15 (1.33)

Outcome	Regular moderate/high dose ICS/LABA, Baseline, N = 575	Regular moderate/high dose ICS/LABA, 52 week, N = 575	Regular high dose ICS, Baseline, N = 133	Regular high dose ICS, 52 week, N = 133
Lung Function (FEV1) (Litres) Change scores, ICS/LABA n=555, ICS n=132 Mean (SD)	NA (NA)	0.18 (0.24)	NA (NA)	0.08 (0.02)
Lung function (morning PEF) (Litres per minute) Change scores, ICS/LABA n=571, ICS n=132 Mean (SD)	NA (NA)	38.78 (39.91)	NA (NA)	5.61 (35.47)

Rescue/reliever medication use - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (morning PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate/high dose ICS/LABA, Baseline, N = 575	Regular moderate/high dose ICS/LABA, 52 week, N = 575	Regular high dose ICS, Baseline, N = 133	Regular high dose ICS, 52 week, N = 133
Severe asthma exacerbations Number of participants with at least one event No of events	n = NA ; % = NA	n = 73 ; % = 12.7	n = NA ; % = NA	n = 29 ; % = 21.8
Mortality No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Regular moderate/high dose ICS/LABA, Baseline, N = 575	Regular moderate/high dose ICS/LABA, 52 week, N = 575	Regular high dose ICS, Baseline, N = 133	Regular high dose ICS, 52 week, N = 133
Adverse events Final values No of events	n = NA ; % = NA	n = 495 ; % = 86	n = NA ; % = NA	n = 118 ; % = 89
Pneumonia (lower respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 18 ; % = 3	n = NA ; % = NA	n = 8 ; % = 6

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Pneumonia (lower respiratory tract infections) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not monitored, 20% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not monitored, 20% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(morningPEF)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not monitored, 20% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not monitored, 20% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Rescue/relievermedicationuse-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not monitored, 20% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not monitored, 20% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia(lowerrespiratorytractinfections)-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Adherence not monitored, 20% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Indirectly applicable

Price, 2003

Bibliographic Reference	Price, D B; Hernandez, D; Magyar, P; Fiterman, J; Beeh, K M; James, I G; Konstantopoulos, S; Rojas, R; van Noord, J A; Pons, M; Gilles, L; Leff, J A; Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma.; Thorax; 2003; vol. 58 (no. 3); 211-6

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	No additional information
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Merck and Co Inc
Inclusion criteria	Non-smokers, or ex-smokers who had stopped for ≥6 months and <12 pack-year history Diagnosed with asthma for >1-year

	Aged 15-75 years Not optimally controlled despite regular ICS treatment with 600–1200 µg/ day budesonide, beclomethasone, triamcinolone or flunisolide, or 300–800 µg/day fluticasone FEV1 ≥50% of predicted and ≥12% improvement after SABA Symptoms requiring SABA use at least once per day during the final two weeks of the run-in period
Exclusion criteria	Other active pulmonary disorders Respiratory tract infection within three weeks Emergency treatment within two months Systemic corticosteroid within a month Received cromones, leukotriene receptor antagonists within two weeks, long acting antihistamine within a week, or LABA or anticholinergic agents within a day
Recruitment / selection of participants	No additional information
Intervention(s)	Following a four-week run-in period where all participants received 800 mcg budesonide, taken as two inhalations of 200 mcg twice per day, those allocated to the intervention received an additional 10 mg on top of the 800 mcg budesonide with SABA as-needed for symptom relief
Population subgroups	Exacerbations 41.4% received ≥1 oral corticosteroid courses in the past year

	Atopy Not reported
Comparator	Following a four-week run-in period where all participants received 800 mcg budesonide, taken as two inhalations of 200 mcg twice per day, those allocated to the comparator received 1600 mcg budesonide with SABA as-needed for symptom relief
Number of participants	889 randomised 448 allocated to ICS+montelukast, 428 completed 441 allocated to ICS, 415 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Intention to treat

Study arms

Regular moderate dose ICS plus montelukast (N = 448)
800 mcg budesonide plus 10 mg montelukast per day

Regular high dose ICS (N = 441)
1600 mcg budesonide per day

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS plus montelukast (N = 448)	Regular high dose ICS (N = 441)
% Female Sample size	n = 288 ; % = 59	n = 269 ; % = 61
Mean age (SD) Mean (SD)	43 (14)	43 (14)
White Sample size	n = 346 ; % = 77.2	n = 338 ; % = 76.6
Black Sample size	n = 2 ; % = 0.4	n = 4 ; % = 0.9
Asian Sample size	n = 24 ; % = 5.4	n = 20 ; % = 4.5
Other Sample size	n = 76 ; % = 17	n = 79 ; % = 17.9
Comorbidities Nominal	NR	NR
ICS dose (µg/day) Mean (SD)	730 (238)	746 (237)

Characteristic	Regular moderate dose ICS plus montelukast (N = 448)	Regular high dose ICS (N = 441)
Asthma control (Puffs per day) SABA use Mean (SD)	2.7 (2.4)	2.7 (2.2)
FEV1 % of predicted Mean (SD)	69 (13.3)	68.3 (13.4)
PEF L/min Mean (SD)	385 (130)	383 (133)

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous Outcomes

Outcome	Regular moderate dose ICS plus montelukast, Baseline, N = 448	Regular moderate dose ICS plus montelukast, 12 week, N = 448	Regular high dose ICS, Baseline, N = 441	Regular high dose ICS, 12 week, N = 441
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 7 ; % = 1.6	n = NA ; % = NA	n = 10 ; % = 2.3

Outcome	Regular moderate dose ICS plus montelukast, Baseline, N = 448	Regular moderate dose ICS plus montelukast, 12 week, N = 448	Regular high dose ICS, Baseline, N = 441	Regular high dose ICS, 12 week, N = 441
Adverse events Final values No of events	n = NA ; % = NA	n = 166 ; % = 37.1	n = NA ; % = NA	n = 182 ; % = 41.3

Severe asthma exacerbations - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Contrast Outcomes

Outcome	Regular moderate dose ICS plus montelukast vs Regular high dose ICS, Baseline, N2 = 441, N1 = 448	Regular moderate dose ICS plus montelukast vs Regular high dose ICS, 12 week, N2 = 441, N1 = 448
Lung function (PEF) (L/min) Change scores Mean (95% CI)	NA (NA to NA)	-3.4 (-12.9 to 4.8)
Reliever/rescue medication use (Puffs per day) Change scores Mean (95% CI)	NA (NA to NA)	0.19 (0.03 to 0.44)

Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-dose ICS plus montelukast-Regular high-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to interventions not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-dose ICS plus montelukast-Regular high-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to interventions not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Lungfunction(PEF)-MeanNineFivePercentCI-Regular moderate-dose ICS plus montelukast-Regular high-dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to interventions not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Reliever/rescuemedicationuse-MeanNineFivePercentCI-Regular moderate dose ICS plus montelukast-Regular high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to interventions not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Price, 2011

Bibliographic Reference	Price, D.; Musgrave, S.; Wilson, E.; Sims, E.; Shepstone, L.; Blyth, A.; Murdoch, J.; Mugford, M.; Juniper, E.; Ayres, J.; Wolfe, S.; Freeman, D.; Lipp, A.; Gilbert, R.; Harvey, I.; A pragmatic single-blind randomised controlled trial and economic evaluation of the use of leukotriene receptor antagonists in primary care at steps 2 and 3 of the national asthma guidelines (ELEVATE study); Health Technology Assessment; 2011; vol. 15 (no. 21); 1-132

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	ELEVATE - ISRCTN99132811
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Primary care and general practices
Study dates	October 2001 - January 2007
Sources of funding	Funded by NIHR
Inclusion criteria	Aged 12-80 years

	Diagnosis of asthma confirmed by bronchodilator reversibility, PEF variability, physician diagnosis or previous response to treatment Receiving ICS for ≥12 weeks PEF >50% of predicted Score ≥1-6 on the ACQ
Exclusion criteria	Received LABA or leukotriene antagonist within 12 weeks Substantial change in asthma medication in last 12 weeks Other active, acute or chronic pulmonary disorder or unresolved respiratory infection within 12 weeks Received systemic corticosteroids within 2 weeks
Recruitment / selection of participants	Recruited from 53 primary care centres and general practices via mailing
Intervention(s)	Participants allocated to the ICS plus montelukast arm received either 10 mg montelukast once daily or 20 mg zafirlukast twice daily in addition to their current ICS treatment. All drug choices were made according to normal clinical practice in-line with BTS guidelines. **Additional medications:** SABA was permitted throughout the study as-needed. Theophylline, cromoglycate, nedocromil and ipratropium were permitted if clinically appropriate. ICS was able to be down-titrated, or removed if the participant was able to manage

	without. LABA was not permitted in this study arm. If a participant required a disallowed medication this was noted, but the participant was able to remain in the trial. *Paper includes two study steps - step 2 does not contain a relevant population or intervention to this review and is not included*
Population subgroups	**Exacerbations** Mixed - average 0.18 and 0.24 in past year in ICS + montelukast and ICS/LABA arms, respectively **Atopy** Not reported
Comparator	Participants allocated to the ICS/LABA arm received either salmeterol or formoterol in addition to their current ICS treatment. All drug choices were made according to normal clinical practice in-line with BTS guidelines. **Additional medications:** SABA was permitted throughout the study as-needed. Theophylline, cromoglycate, nedocromil and ipratropium were permitted if clinically appropriate. ICS was able to be down-titrated, or removed if the participant was able to manage without. LTRAs were not permitted in this study arm. If a participant required a disallowed medication this was noted, but the participant was able to remain in the trial.
Number of participants	352 randomised 170 allocated to ICS + montelukast 182 allocated to ICS/LABA

Duration of follow-up	2 years
Indirectness	Downgraded by two increments due to intervention indirectness - could have been treated with either montelukast or zafirlukast, protocol specified montelukast, and flexible dosing of ICS throughout the study
Additional comments	ITT using multiple imputation for missing data

Study arms

Regular low/moderate dose ICS plus montelukast (N = 170)

10 mg montelukast or 20 mg zafirlukast in addition to pre-study ICS, which could be down-titrated or removed at the study investigators discretion

Regular low/moderate dose ICS/LABA (N = 182)

Salmeterol or formoterol added to pre-study ICS, which could be down-titrated, but not removed, at the study investigators discretion

Characteristics

Arm-level characteristics

Characteristic	Regular low/moderate dose ICS plus montelukast (N = 170)	Regular low/moderate dose ICS/LABA (N = 182)
% Female Sample size	n = 109 ; % = 64	n = 111 ; % = 61
Mean age (SD) Mean (SD)	51 (16)	49.7 (16.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Regular low/moderate dose ICS plus montelukast (N = 170)	Regular low/moderate dose ICS/LABA (N = 182)
Caucasian Sample size	n = 168 ; % = 99	n = 178 ; % = 98
Non-Caucasian Sample size	n = 0 ; % = 0	n = 2 ; % = 1
Unknown Sample size	n = 2 ; % = 1	n = 2 ; % = 1
Comorbidities Nominal	NR	NR
ICS dose Mean (SD)	425 (351)	451 (390)
Asthma control Mean (SD)	NA (NA)	NA (NA)
ACQ score Mean (SD)	2.01 (0.85)	2.19 (0.87)
Average SABA uses per day in past year Mean (SD)	4.3 (4)	4.4 (3.5)

Characteristic	Regular low/moderate dose ICS plus montelukast (N = 170)	Regular low/moderate dose ICS/LABA (N = 182)
Lung function (% of predicted) PEF Median (IQR)	90.46 (80.24 to 99.67)	88.64 (76.67 to 99.89)

Outcomes

Study timepoints

- Baseline
- 2 year

Continuous Outcomes

Outcome	Regular low/moderate dose ICS plus montelukast, Baseline, N = 176	Regular low/moderate dose ICS plus montelukast, 2 year, N = 169	Regular low/moderate dose ICS/LABA, Baseline, N = 185	Regular low/moderate dose ICS/LABA, 2 year, N = 181
Quality of life (MiniAQLQ) Final values, scale range: 1-7 Mean (SD)	4.63 (1.03)	5.43 (1.14)	4.41 (1.04)	5.42 (1.08)
Quality of life (EQ-5D) Final values, scale range: 0-1, ICS+Mont n=160, ICS/LABA n=170 Mean (SD)	0.78 (0.24)	0.81 (0.26)	0.77 (0.23)	0.8 (0.27)
Reliver/rescue medication use (daytime reliever use)	2.73 (2.59)	1.89 (2.31)	2.74 (2.01)	1.49 (1.65)

Outcome	Regular low/moderate dose ICS plus montelukast, Baseline, N = 176	Regular low/moderate dose ICS plus montelukast, 2 year, N = 169	Regular low/moderate dose ICS/LABA, Baseline, N = 185	Regular low/moderate dose ICS/LABA, 2 year, N = 181
(Puffs per day) Final values, ICS+Mont n=84, ICS/LABA n=95 Mean (SD)				
Reliever/rescue medication use (night-time reliever use) (Puffs per night) Final values, ICS+Mont n=75, ICS/LABA n=87 Mean (SD)	0.95 (1.42)	0.69 (1.04)	0.91 (1.01)	0.63 (0.87)
Lung function (PEF) (L/min) Final values, ICS+Mont n=83, ICS/LABA n=98 Mean (SD)	391.1 (101.5)	395.6 (105.9)	393.7 (104.7)	419.8 (97)
Asthma control (ACQ) Final values, scale range: 0-6 Mean (SD)	2.01 (0.85)	1.31 (0.96)	2.19 (0.87)	1.34 (0.92)

Quality of life (MiniAQLQ) - Polarity - Higher values are better
Quality of life (EQ-5D) - Polarity - Higher values are better
Reliver/rescue medication use (daytime reliever use) - Polarity - Lower values are better
Reliever/rescue medication use (night-time reliever use) - Polarity - Lower values are better
Lung function (PEF) - Polarity - Higher values are better
Asthma control (ACQ) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Regular low/moderate dose ICS plus montelukast, Baseline, N = 176	Regular low/moderate dose ICS plus montelukast, 2 year, N = 176	Regular low/moderate dose ICS/LABA, Baseline, N = 185	Regular low/moderate dose ICS/LABA, 2 year, N = 185
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Hospital admissions Final values No of events	n = NA ; % = NA	n = 3 ; % = 2	n = NA ; % = NA	n = 5 ; % = 3

Mortality - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better

Contrast Outcomes

Outcome	Regular low/moderate dose ICS plus montelukast vs Regular low/moderate dose ICS/LABA, Baseline, N2 = 182, N1 = 170	Regular low/moderate dose ICS plus montelukast vs Regular low/moderate dose ICS/LABA, 2 year, N2 = 182, N1 = 170
Severe exacerbation rate Final values, rate ratio Mean (95% CI)	NA (NA to NA)	1.02 (0.74 to 1.41)

Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
ContinuousOutcomes-Qualityoflife(MiniAQLQ)-MeanSD-Regular low-dose ICS plus montelukast-Regular moderate-high dose ICS/LABA-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(~86% adherence to study medications, use of additional unrandomised medications in 31% of participants and subjective outcome measure assessed in an open label study design)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Qualityoflife(EQ-5D)-MeanSD-Regular low-dose ICS plus montelukast-Regular moderate-high dose ICS/LABA-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(~86% adherence to study medications, use of additional unrandomised medications in 31% of participants and subjective outcome measure assessed in an open label study design)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Asthmacontrol(ACQ)-MeanSD-Regular low-dose ICS plus montelukast-Regular moderate-high dose ICS/LABA-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(~86% adherence to study medications, use of additional unrandomised medications in 31% of participants and subjective outcome measure assessed in an open label study design)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliver/rescuemedicationuse(daytimerelieveruse)-MeanSD-Regular low-dose ICS plus montelukast-Regular moderate-high dose ICS/LABA-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(~86% adherence to study medications and use of additional unrandomised medications in 31% of participants and high dropout rate and no information on differences between ITT and PP data)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliever/rescuemedicationuse(night-timerelieveruse)-MeanSD-Regular low-dose ICS plus montelukast-Regular moderate-high dose ICS/LABA-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(~86% adherence to study medications and use of additional unrandomised medications in 31% of participants and high dropout rate and no information on differences between ITT and PP data)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(PEF)-MeanSD-Regular low-dose ICS plus montelukast-Regular moderate-high dose ICS/LABA-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(~86% adherence to study medications and use of additional unrandomised medications in 31% of participants and high dropout rate and no information on differences between ITT and PP data)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular low-dose ICS plus montelukast-Regular moderate-high dose ICS/LABA-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(~86% adherence to study medications and use of additional unrandomised medications in 31% of participants)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Hospitaladmissions-NoOfEvents-Regular low-dose ICS plus montelukast-Regular moderate-high dose ICS/LABA-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(~86% adherence to study medications and use of additional unrandomised medications in 31% of participants)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Severeexacerbationrate-MeanNineFivePercentCI-Regular low/moderate dose ICS plus montelukast-Regular low/moderate dose ICS/LABA-t2

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(~86% adherence to study medications and use of additional unrandomised medications in 31% of participants)*
Overall bias and Directness	Overall Directness	Directly applicable

Scicchitano, 2004

Bibliographic Reference	Scicchitano, R; Aalbers, R; Ukena, D; Manjra, A; Fouquert, L; Centanni, S; Boulet, L-P; Naya, I P; Hultquist, C; Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma.; Current medical research and opinion; 2004; vol. 20 (no. 9); 1403-18

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	International multicentre (Argentina, Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Mexico, The Netherlands, New Zealand, Norway, Portugal, Russia, South Africa, Turkey.
Study setting	Multicentre (211 centres); outpatient hospital/primary care setting
Study dates	May 2001 - January 2003
Sources of funding	Supported by AstraZeneca
Inclusion criteria	Aged 12-80 years Diagnosis of asthma for ≥6 months (as defined by the American Thoratic Society)

	History of ≥1 clinically important exacerbation in the past year Receiving ICS at a dose of 400-1600 mcg per day for ≥3 months and at a constant dose for ≥30 days pre-study FEV1 50-90% of predicted ≥12% reversibility of FEV1 after receiving SABA Symptomatic with moderate-severe asthma (according to medication needs) during run-in.
Exclusion criteria	Received systemic corticosteroids or inhaled cromones within ≤30 days Taken ≥3 courses of oral steroids in the past 6 months Cardiovascular disease or any other significant disorder Experienced a respiratory tract infection within the past 30 days Smokers with a smoking history of >10 pack years >10 SABA uses on any day of the run-in
Recruitment / selection of participants	Recruited from outpatient departments of 211 hospitals/primary care settings in Argentina, Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Mexico, the Netherlands, New Zealand, Norway, Portugal, Russia, South Africa and Turkey - method not reported
Intervention(s)	Following a two-week run-in period where participants received their regular ICS treatment and took inhalations of terbutaline 0.5mg as needed administered via a Turbuhaler, participants who were symptomatic and had moderate to severe astghma based on their level of treatment and a history of clinically important exacerbations were randomised. Those randomised to receive ICS/formoterol received 160/4.5 mcg budesonide/formoterol, two inhalations once daily in the evening, plus additional inhalations as-needed for symptom relief up to a maximum of ten inhalations per day.
Population subgroups	Exacerbations

	Yes - exacerbation within past-year was an inclusion criteria Atopy Not reported
Comparator	Following a two-week run-in period where participants received their regular ICS treatment and took inhalations of terbutaline 0.5mg as needed administered via a Turbuhaler, participants who were symptomatic and had moderate to severe astghma based on their level of treatment and a history of clinically important exacerbations were randomised. Those randomised to receive ICS received 160 mcg budesonide, two inhalations twice daily in the morning and evening, plus 0.4 mg terbutaline as-needed for symptom relief up to a maximum of ten inhalations per day
Number of participants	1890 randomised 947 received regular plus as-needed ICS/formoterol 943 received regular ICS
Duration of follow-up	12 months
Indirectness	None
Additional comments	Intention to treat

Study arms

Low dose ICS/formoterol MART (N = 947)
160/4.5 mcg budesonide/formoterol, two inhalations once daily, plus additional inhalations as-needed for symptom relief

Regular moderate dose ICS (N = 943)
160 mcg budesonide, two inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Low dose ICS/formoterol MART (N = 947)	Regular moderate dose ICS (N = 943)
% Female Sample size	n = 554 ; % = 59	n = 538 ; % = 57
Mean age (SD) Nominal	43	43
Mean age (SD) Range	12 to 79	11 to 80
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Mean (range) Nominal	744	748
ICS dose Mean (range) Range	250 to 2000	400 to 2000

Characteristic	Low dose ICS/formoterol MART (N = 947)	Regular moderate dose ICS (N = 943)
Asthma control Average (range) number of SABA uses per day Nominal	1.9	2
Asthma control Average (range) number of SABA uses per day Range	0 to 15.6	0 to 9.2
Lung function (% of predicted) Mean (range) FEV1 Nominal	70	70
Lung function (% of predicted) Mean (range) FEV1 Range	46 to 102	37 to 95

Outcomes

Study timepoints

- Baseline
- 12 month

Dichotomous Outcomes

Outcome	Low dose ICS/formoterol MART, Baseline, N = 947	Low dose ICS/formoterol MART, 12 month, N = 947	Regular moderate dose ICS, Baseline, N = 943	Regular moderate dose ICS, 12 month, N = 943
Severe asthma exacerbations	n = NA ; % = NA	n = 137 ; % = 14	n = NA ; % = NA	n = 212 ; % = 22

Outcome	Low dose ICS/formoterol MART, Baseline, N = 947	Low dose ICS/formoterol MART, 12 month, N = 947	Regular moderate dose ICS, Baseline, N = 943	Regular moderate dose ICS, 12 month, N = 943
Number of participants with at least one event No of events				
Mortality No of events	n = NA ; % = NA	n = 1 ; % = 1	n = NA ; % = NA	n = 2 ; % = 1
Adverse events Final values No of events	n = NA ; % = NA	n = 526 ; % = 56	n = NA ; % = NA	n = 533 ; % = 57

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Contrast Outcomes

Outcome	Low dose ICS/formoterol MART vs Regular moderate dose ICS, Baseline, N2 = NA, N1 = NA	Low dose ICS/formoterol MART vs Regular moderate dose ICS, 12 month, N2 = 947, N1 = 943
Lung function (PEF) (Litres per minute) Change scores Mean (95% CI)	NA (NA to NA)	20.3 (16.5 to 24.1)
Reliever/rescue medication use (SABA-free days) (%) Change scores Mean (95% CI)	NA (NA to NA)	11 (8.2 to 13.8)

Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use (SABA-free days) - Polarity - Higher values are better

Continuous Outcomes

Outcome	Low dose ICS/formoterol MART, Baseline, N = 943	Low dose ICS/formoterol MART, 12 month, N = 943	Regular moderate dose ICS, Baseline, N = 947	Regular moderate dose ICS, 12 month, N = 947
Severe exacerbation rate Total number of events, final values Nominal	NA	197	NA	349

Severe exacerbation rate - Polarity - Lower values are better
Severe exacerbations extracted as those requiring systemic corticosteroids or hospitalisation/ER treatment

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular low-dose ICS/formoterol with ICS/formoterol Prn-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(paper reports there were 397 protocol deviations (in 306 patients (16%)) e.g. due to randomisation error (4%), the rest not specified)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular low-dose ICS/formoterol with ICS/formoterol Prn-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(paper reports there were 397 protocol deviations (in 306 patients (16%)) e.g. due to randomisation error (4%), the rest not specified)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular low-dose ICS/formoterol with ICS/formoterol Prn-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(paper reports there were 397 protocol deviations (in 306 patients (16%)) e.g. due to randomisation error (4%), the rest not specified)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Lungfunction(PEF)-MeanNineFivePercentCI-Regular low-dose ICS/formoterol with ICS/formoterol Prn-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(paper reports there were 397 protocol deviations (in 306 patients (16%)) e.g. due to randomisation error (4%), the rest not specified)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Reliever/rescuemedicationuse(SABA-freedays)-MeanNineFivePercentCI-Regular low-dose ICS/formoterol with ICS/formoterol Prn-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(paper reports there were 397 protocol deviations (in 306 patients (16%)) e.g. due to randomisation error (4%), the rest not specified)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Severeexacerbationrate-Nominal-Low dose ICS/formoterol MART-Regular moderate dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(paper reports there were 397 protocol deviations (in 306 patients (16%)) e.g. due to randomisation error (4%), the rest not specified)*
Overall bias and Directness	Overall Directness	Directly applicable

Shapiro, 2000

Bibliographic Reference	Shapiro, G.; Lumry, W.; Wolfe, J.; Given, J.; White, M.V.; Woodring, A.; Baitinger, L.; House, K.; Prillaman, B.; Shah, T.; Combined salmeterol 50 mug and fluticasone propionate 250 in the diskus device for the treatment of asthma; American Journal of Respiratory and Critical Care Medicine; 2000; vol. 161 (no. 2i); 527-534

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Glaxo Wellcome
Inclusion criteria	≥12 years of age Diagnosis of asthma requiring pharmacotherapy for at least 6 months

	FEV1 40-85% of predicted ≥15% increase in FEV1 after receiving SABA Received ICS continuously for at least 12 weeks and at a constant dose for at least 4 weeks (beclomethasone dipropionate (462-672 mcg/d), triamcinolone acetonide (1,100-1,600 mcg/d), flunisolide (1,250-2,000 mcg/d), fluticasone propionate (440 mcg/d)
Exclusion criteria	History of life threatening asthma Smoking history >10 pack years Use of systemic corticosteroids within a month Use of daily oral corticosteroids within 6 months Concurrent use of any medications that could affect study medications Abnormal chest radiograph or ECG History of significant concurrent disease (diabetes, hypertension, glaucoma etc.) >3 night awakenings requiring SABA or >12 puffs of SABA daily for >3 days during the 7 days pre-randomisation
Recruitment / selection of participants	Recruited from 42 sites, method not reported
Intervention(s)	Participants allocated to the ICS/LABA arm received 250/50 mcg fluticasone propionate/salmeterol, one inhalation twice per day, via a Diskus inhaler. Participants were provided with albuterol to be taken as-needed for symptom relief.
Population subgroups	**Exacerbations**

	Not reported **Atopy** Not reported
Comparator	Participants allocated to the ICSarm received 250 mcg fluticasone propionate, one inhalation twice per day, via a Diskus inhaler. Participants were provided with albuterol to be taken as-needed for symptom relief. *Study also contained arms where participants received salmeterol monotherapy or placebo, excluded from this review due to not containing relevant interventions*
Number of participants	349 randomised 84 allocated to ICS/LABA, 68 completed 84 allocated to ICS, 59 completed 88 allocated to LABA (excluded from this review) 93 allocated to placebo (excluded from this review)
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular moderate dose ICS/LABA (N = 84)
250/50 mcg fluticasone propionate/salmeterol twice daily

Regular moderate dose ICS (N = 84)
250 mcg fluticasone propionate twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 84)	Regular moderate dose ICS (N = 84)
% Female Sample size	n = 44 ; % = 52	n = 39 ; % = 46
Mean age (SD) Nominal	38	40
Mean age (SD) Range	12 to 69	12 to 67
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 61 ; % = 73	n = 75 ; % = 89
Other Sample size	n = 23 ; % = 27	n = 9 ; % = 11

Characteristic	Regular moderate dose ICS/LABA (N = 84)	Regular moderate dose ICS (N = 84)
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Nominal	69	66

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 81	Regular moderate dose ICS/LABA, 12 week, N = 81	Regular moderate dose ICS, Baseline, N = 81	Regular moderate dose ICS, 12 week, N = 81
Reliever medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-2.3 (3.6)	NA (NA)	-0.9 (1.8)

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 81	Regular moderate dose ICS/LABA, 12 week, N = 81	Regular moderate dose ICS, Baseline, N = 81	Regular moderate dose ICS, 12 week, N = 81
Lung Function (FEV1) (Litres) Change scores Mean (SD)	NA (NA)	0.48 (0.45)	NA (NA)	0.25 (0.45)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	53.5 (50.4)	NA (NA)	15.2 (41.4)

Reliever medication use - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 81	Regular moderate dose ICS/LABA, 12 week, N = 81	Regular moderate dose ICS, Baseline, N = 81	Regular moderate dose ICS, 12 week, N = 81
Adrenal insufficiency (morning cortisol <5µg/dL) Final values No of events	n = 0 ; % = 0	n = 1 ; % = 3	n = 1 ; % = 3	n = 2 ; % = 6

Adrenal insufficiency (morning cortisol <5µg/dL) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Relievermedicationuse-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 22% missing data, 11% difference in missing data rates between study arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 22% missing data, 11% difference in missing data rates between study arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(PEF)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 22% missing data, 11% difference in missing data rates between study arms and reasons for discontinuation related to participant's health status)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adrenalinsufficiency(morningcortisol<5µg/dL)-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 22% missing data, 11% difference in missing data rates between study arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Sher, 2017

Bibliographic Reference	Sher, Lawrence D; Yiu, Gloria; Sakov, Anat; Liu, Siyu; Caracta, Cynthia F; Fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers compared with placebo for persistent asthma.; Allergy and asthma proceedings; 2017; vol. 38 (no. 5); 343-353

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT02141854
Study type	Randomised controlled trial (RCT)
Study location	Multinational - USA, Canada, Czech Republic, Hungary, Poland, Russia, South Africa and Ukraine
Study setting	No additional information
Study dates	October 2014 - September 2015
Sources of funding	Sponsored by Teva Branded Pharmaceuticals R&D
Inclusion criteria	≥12 years of age Diagnosis of persistent asthma (symptoms or reliever medication use >2 days per week or night awakenings >3 times a month)

	FEV1 40-85% of predicted and ≥15% and 200mL reversibility after receiving SABA Receiving ICS, with or without a LABA, at a dose >200 mcg fluticasone propionate per day for ≥1 month
Exclusion criteria	Pregnant, breastfeeding or not using contraception History of life threatening asthma Asthma exacerbation requiring systemic corticosteroids within 30 days Hospitalisation for asthma within 2 months Use of immunosuppressive medication within 4 weeks Planned initiation or escalation of immunotherapy during the study period Bacterial or viral respiratory infection within 2 weeks Current smoking, history >10 pack years or use of tobacco products within a year
Recruitment / selection of participants	Recruited from 147 centres, method not reported
Intervention(s)	Following a 2-3 week run-in period during which participants received 50 mcg fluticasone propionate twice daily, those allocated to the ICS/LABA arm received 200/12.5 mcg fluticasone propionate/salmeterol, one inhalation twice per day

	Study also included an arm containing 100/12.5 mcg fluticasone propionate/salmeterol, excluded from this review due to not being a moderate-high dose ICS/LABA combination
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Following a 2-3 week run-in period during which participants received 50 mcg fluticasone propionate twice daily, those allocated to the ICS arm received 200 mcg fluticasone propionate, one inhalation twice per day *Study also included an arm containing 100 mcg fluticasone propionate, excluded from this review due to not being a moderate-high dose ICS, and a placebo arm, excluded due to not being a relevant comparator*
Number of participants	728 randomised 146 allocated to ICS/LABA 146 allocated to ICS 145 allocated to low-dose ICS/LABA (excluded from this review) 146 allocated to low-dose ICS (excluded from this review) 145 allocated to placebo (excluded from this review)
Duration of follow-up	12 weeks

Indirectness	None
Additional comments	ITT

Study arms

Regular moderate dose ICS (N = 146)
200 mcg fluticasone propionate, one inhalation twice daily

Regular moderate dose ICS/LABA (N = 146)
200/25 mcg fluticasone propionate/salmeterol, one inhalation twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS (N = 146)	Regular moderate dose ICS/LABA (N = 146)
% Female Sample size	n = 88 ; % = 60	n = 87 ; % = 60
Mean age (SD) Mean (SD)	44.4 (16.4)	44.7 (16.9)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 116 ; % = 79	n = 125 ; % = 86
Black or African American	n = 23 ; % = 16	n = 20 ; % = 14

Characteristic	Regular moderate dose ICS (N = 146)	Regular moderate dose ICS/LABA (N = 146)
Sample size		
Asian Sample size	n = 2 ; % = 1	n = 0 ; % = 0
Other Sample size	n = 5 ; % = 3	n = 1 ; % = 0
Comorbidities Nominal	NR	NR
ICS dose Sample size	n = NA ; % = NA	n = NA ; % = NA
ICS Sample size	n = 64 ; % = 43	n = 73 ; % = 50
ICS/LABA Sample size	n = 83 ; % = 57	n = 73 ; % = 50
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	64 (10)	65 (11)

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous Outcomes

Outcome	Regular moderate dose ICS, Baseline, N = 146	Regular moderate dose ICS, 12 week, N = 146	Regular moderate dose ICS/LABA, Baseline, N = 146	Regular moderate dose ICS/LABA, 12 week, N = 146
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 58 ; % = 40	n = NA ; % = NA	n = 58 ; % = 40
Pneumonia (respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 3 ; % = 2	n = NA ; % = NA	n = 2 ; % = 1

Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Pneumonia (respiratory tract infections) - Polarity - Lower values are better

Contrast Outcomes

Outcome	Regular moderate dose ICS/LABA vs Regular moderate dose ICS, Baseline, N2 = 146, N1 = 145	Regular moderate dose ICS/LABA vs Regular moderate dose ICS, 12 week, N2 = 146, N1 = 145
Quality of life (Asthma quality of life questionnaire with standard activities) Scale range: 1-7, change scores Mean (p value)	NA (NA)	0.15 (0.15)
Reliever/rescue medication use (Puffs per day) Change scores Mean (p value)	NA (NA)	-0.36 (0.016)
Lung Function (FEV1) (Litres) Change scores Mean (p value)	NA (NA)	0.093 (0.0309)
Lung function (PEF) (Litres per minute) Change scores Mean (p value)	NA (NA)	13 (0.0002)

Quality of life (Asthma quality of life questionnaire with standard activities) - Polarity - Higher values are better
Reliever/rescue medication use - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better
FEV1: ICS n=145; AQLQ: ICS/LABA n=131, ICS n=132

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia(respiratorytractinfections)-NoOfEvents-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to treatment not monitored)*
Overall bias and Directness	Overall Directness	Indirectly applicable

ContrastOutcomes-Qualityoflife(Asthmaqualityoflifequestionnairewithstandardactivities)-MeanPValue-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Reliever/rescuemedicationuse-MeanPValue-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-LungFunction(FEV1)-MeanPValue-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Lungfunction(PEF)-MeanPValue-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Randomisation method not reported and adherence to treatment not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Spector, 2012

Bibliographic Reference	Spector, Sheldon L; Martin, Ubaldo J; Uryniak, Tom; O'Brien, Christopher D; Budesonide/formoterol pressurized metered-dose inhaler versus budesonide: a randomized controlled trial in black patients with asthma.; The Journal of asthma : official journal of the Association for the Care of Asthma; 2012; vol. 49 (no. 1); 70-7

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00702325
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	June 2008 - September 2009
Sources of funding	Supported by AstraZeneca
Inclusion criteria	≥12 years of age Black ethnicity

	Asthma diagnosis for ≥6 months FEV1 45-85% of predicted FEV1 reversibility ≥12% and ≥0.20 L after receiving SABA Receiving ICS at a moderate-high dose for ≥30 days prior to screening Symptomatic (daytime or nighttime symptom scores >0 on ≥3 out of 7 consecutive days) during 2-week run-in period
Exclusion criteria	≥1 asthma-related hospitalisation in the past 6 months >1 asthma-related emergency department visit in the past 3 months Systemic corticosteroid treatment in the past 30 days Omalizumab treatment in the past 90 days
Recruitment / selection of participants	Recruited from 46 centres, method not reported
Intervention(s)	Following a two-week run-in period where participants received 90 mcg budesonide, two inhalations twice daily, those randomised to the ICS/LABA arm received 160/4.5 mcg budesonide/formoterol, two inhalations twice daily plus salbutamol as-needed for symptom relief
Population subgroups	Exacerbations Not reported

	Atopy Not reported
Comparator	Following a two-week run-in period where participants received 90 mcg budesonide, two inhalations twice daily, those randomised to the ICS arm received 180 mcg budesonide, two inhalations twice daily, plus salbutamol as-needed for symptom relief
Number of participants	311 randomised 156 received ICS/LABA, 118 completed 155 received ICS monotherapy, 102 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Available case analysis

Study arms

Regular moderate dose ICS/LABA (N = 153)
160/4.5 mcg budesonide/formoterol, two inhalations twice daily

Regular moderate dose ICS (N = 148)
180 mcg budesonide, two inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 153)	Regular moderate dose ICS (N = 148)
% Female Sample size	n = 109 ; % = 71	n = 87 ; % = 59
Mean age (SD) Mean (SD)	38.6 (13)	39.8 (15.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
African Sample size	n = 3 ; % = 2	n = 5 ; % = 3
African American Sample size	n = 143 ; % = 94	n = 137 ; % = 93
African Caribbean Sample size	n = 7 ; % = 5	n = 6 ; % = 4
Comorbidities Nominal	NR	NR
ICS dose Sample size	n = NA ; % = NA	n = NA ; % = NA
Moderate-dose	n = 107 ; % = 70	n = 97 ; % = 66

Characteristic	Regular moderate dose ICS/LABA (N = 153)	Regular moderate dose ICS (N = 148)
Sample size		
High-dose Sample size	n = 46 ; % = 30	n = 51 ; % = 35
Asthma control Daily SABA inhalations Mean (SD)	2.47 (2.14)	2.04 (2.09)
Lung function (% of predicted) FEV1 Mean (SD)	68.5 (12)	66.8 (12)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 156	Regular moderate dose ICS/LABA, 12 week, N = 156	Regular moderate dose ICS, Baseline, N = 155	Regular moderate dose ICS, 12 week, N = 155
Reliever/rescue medication use (Inhalations per day) Change scores, ICS/LABA n=150, ICS n=144	NA (NA)	-1.27 (1.81)	NA (NA)	-0.62 (1.68)

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 156	Regular moderate dose ICS/LABA, 12 week, N = 156	Regular moderate dose ICS, Baseline, N = 155	Regular moderate dose ICS, 12 week, N = 155
Mean (SD)				
Lung Function (FEV1) (Litres) Change scores, ICS/LABA n=150, ICS n=143 Mean (SD)	NA (NA)	0.16 (0.31)	NA (NA)	0.07 (0.26)
Lung function (morning PEF over last 7 days) (Litres per minute) Change scores, ICS/LABA n=149, ICS n=139 Mean (SD)	NA (NA)	25.3 (43.7)	NA (NA)	7.5 (32.4)
Reliever/rescue medication use (% SABA-free days) Change scores, ICS/LABA n=150, ICS n=144 Mean (SD)	NA (NA)	29.31 (34.13)	NA (NA)	17.7 (35.39)

Reliever/rescue medication use - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better
Lung function (morning PEF over last 7 days) - Polarity - Higher values are better
Reliever/rescue medication use (% SABA-free days) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 156	Regular moderate dose ICS/LABA, 12 week, N = 156	Regular moderate dose ICS, Baseline, N = 155	Regular moderate dose ICS, 12 week, N = 155
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Adverse events No of events	n = NA ; % = NA	n = 63 ; % = 41.2	n = NA ; % = NA	n = 47 ; % = 30.3

Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 29% missing outcome data, 10% difference in dropout rate between study arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliever/rescuemedicationuse-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 29% missing outcome data, 10% difference in dropout rate between study arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(morningPEFoverlast7days)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 29% missing outcome data, 10% difference in dropout rate between study arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliever/rescuemedicationuse(%SABA-freedays)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 29% missing outcome data, 10% difference in dropout rate between study arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 29% missing outcome data, 10% difference in dropout rate between study arms and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Stirbulov, 2012

Bibliographic Reference	Stirbulov, Roberto; Fritscher, Carlos Cezar; Pizzichini, Emilio; Pizzichini, Marcia Margaret Menezes; Evaluation of the efficacy and safety of a fixed-dose, single-capsule budesonide-formoterol combination in uncontrolled asthma: a randomized, double-blind, multicenter, controlled clinical trial.; Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia; 2012; vol. 38 (no. 4); 431-7

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Brazil
Study setting	Four centres in Brazil
Study dates	Recruitment between April 2009 and June 2010; 4 week run-in period and 12 week randomised treatment duration
Sources of funding	None
Inclusion criteria	Patients with partially controlled persistent asthma, as determined on the basis of the classifications proposed by the Global Strategy for Asthma Management and Prevention and the Fourth Brazilian Guidelines for Asthma Management.

	All of the participants had been diagnosed with asthma at least one year prior, had never smoked or had stopped smoking more than one year prior (with a smoking history of fewer than 20 pack-years), and had no other respiratory diseases or comorbidities that could affect the results of the study. None of the participants had received oral corticosteroids or had been hospitalized in the previous month
Exclusion criteria	None specified
Recruitment / selection of participants	Between April of 2009 and June of 2010, 304 adults with asthma were recruited from among those being treated at any of four research centers in Brazil. Of those 304 patients, 181 were included in the study and were randomized into one of the intervention groups; 175 participants used at least one dose of the medication (90 in the budesonide-only group and 85 in the budesonide-formoterol [BF] group), being included in the intention-to-treat analysis.
Intervention(s)	Regular moderate ICS combination with LABA: Fixed-dose, single capsule combination of budesonide 400µg and formoterol 12µg; inhaled administration of dry powder capsule twice daily for 12 weeks. Intervention was received after a run-in period of 4 weeks, during which all participants received 400µg of inhaled budesonide twice daily. Concomitant use of other asthma treatments was not allowed, except for rescue albuterol use and oral corticosteroid use during exacerbations (courses of oral corticosteroid therapy consisting of prednisone 40 mg for 3 days, 20 mg for 3 days, and 10 mg for another 3 days).
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Regular moderate ICS alone: inhaled administration of budesonide 400µg twice daily for 12 weeks; dry powder capsule identical to intervention group.

	Intervention was received after a run-in period of 4 weeks, during which all participants received 400µg of inhaled budesonide twice daily. Concomitant use of other asthma treatments was not allowed, except for rescue albuterol use and oral corticosteroid use during exacerbations (courses of oral corticosteroid therapy consisting of prednisone 40 mg for 3 days, 20 mg for 3 days, and 10 mg for another 3 days).
Number of participants	181 randomised, 175 analysed.
Duration of follow-up	12 weeks
Indirectness	Population indirectness as initially therapy of the participants while they were uncontrolled was not specified.
Additional comments	All of the efficacy variables were evaluated for the participants who received at least one dose of the medication and who underwent at least one post-baseline evaluation of efficacy (intention-to-treat population). The observed values of PEF were recorded in the participant diary. The baseline measurement was represented by the mean of the last 10 values recorded in the run-in period, whereas the final measurement was represented by the mean of the last 10 values recorded in the treatment period. A covariance model was used to evaluate the changes in the spirometric parameters and those in PEF (i.e., the difference between final values and baseline values). In the initial adjusted model, treatment was considered a fixed factor, whereas baseline values, gender, age, and center were considered covariates, as were gender/type of treatment interactions and center/type of treatment interactions. Adjusted mean estimates and 95% CIs were calculated for the final adjusted model, non-significant interactions and covariates being excluded. The last-observation-carried-forward imputation method was used. The efficacy variables representing counts were evaluated by a generalized linear model, the negative binomial distribution being used and the center being considered a covariate.

Study arms

Regular moderate dose ICS/LABA (N = 85)
Fixed dose, single capsule of ICS-LABA combination: budesonide (400µg) -formoterol (12µg), twice daily, delivered via Aerocaps

Regular moderate dose ICS (N = 90)
Budesonide alone (400 µg) twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 85)	Regular moderate dose ICS (N = 90)
% Female Nominal	NR	NR
Mean age (SD) Nominal	NR	NR
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR

Characteristic	Regular moderate dose ICS/LABA (N = 85)	Regular moderate dose ICS (N = 90)
Lung function (% of predicted) FEV1 Mean (SD)	76.5 (NR)	75.9 (NR)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 85	Regular moderate dose ICS/LABA, 12 week, N = 85	Regular moderate dose ICS, Baseline, N = 90	Regular moderate dose ICS, 12 week, N = 90
Lung Function (FEV1) (% of predicted) Change scores Mean (SD)	NA (NA)	0.12 (0.31)	NA (NA)	0.02 (0.31)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	30.19 (49.88)	NA (NA)	6.27 (48.67)

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 85	Regular moderate dose ICS/LABA, 12 week, N = 85	Regular moderate dose ICS, Baseline, N = 90	Regular moderate dose ICS, 12 week, N = 90
Reliever/rescue medication use (SABA-free days) (days) Change scores Mean (SD)	NA (NA)	66.01 (73.71)	NA (NA)	49.02 (51.48)

Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use (SABA-free days) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
ContinuousOutcomes-LungFunction(FEV1)-MeanSD-regular moderate dose ICS/LABA-regular moderate dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Very limited information on baseline characteristics)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population indirectness: initial therapy prior to study is not specified)*

ContinuousOutcomes-Lungfunction(PEF)-MeanSD-regular moderate dose ICS/LABA-regular moderate dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population indirectness: initial therapy prior to study is not specified)*

ContinuousOutcomes-Reliever/rescuemedicationuse(SABA-freedays)-MeanSD-regular moderate dose ICS/LABA-regular moderate dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population indirectness: initial therapy prior to study is not specified)*

Takeyama, 2014

Bibliographic Reference	Takeyama, Kiyoshi; Kondo, Mitsuko; Tagaya, Etsuko; Kirishi, Saori; Ishii, Masanobu; Ochiai, Katsunori; Isono, Kazuo; Tamaoki, Jun; Budesonide/formoterol maintenance and reliever therapy in moderate-to-severe asthma: effects on eosinophilic airway inflammation.; Allergy and asthma proceedings; 2014; vol. 35 (no. 2); 141-7

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	Clinical trial 121104
Study type	Randomised controlled trial (RCT)
Study location	No additional information
Study setting	No additional information
Study dates	No additional information
Sources of funding	No additional information
Inclusion criteria	Outpatients aged 16-80 years Diagnosis of asthma, as per ATS guidelines, for at least 3 months

	Treated with constant dose of ICS (budesonide 320-640 mcg/day, fluticasone 200-500 mcg/day) plus LABA for ≥3 months History of one or more exacerbations in the previous year Asthma Control Test score ≤20 Reliever medication use ≥5 times a week FEV1 60-100% of predicted, with ≥12% reversibility
Exclusion criteria	Significant concomitant disorder, such as cardiovascular disease Current or previous smokers with a history of >10 pack-years Pregnant or breast feeding
Recruitment / selection of participants	No additional information
Intervention(s)	Following a run-in period, participant allocated to the intervention received a 160/4.5 mcg budesonide/formoterol inhaler which was inhaled twice, two times per day, plus additional inhalations as-needed for symptom relief up to a maximum of four additional inhalations per day.
Population subgroups	**Exacerbations** Yes - inclusion criteria specified ≥1 in past year **Atopy** Not reported

Comparator	Following a run-in period, participant allocated to the comparator received a 160/4.5 mcg budesonide/formoterol inhaler which was inhaled twice, two times per day. Participants also received a 100 mcg salbutamol inhaler which was used as-needed for symptom relief up to a maximum of four inhalations per day.
Number of participants	63 randomised 32 received BUD/FORM + BUD/FORM 21 received BUD/FORM + salbutamol Attrition not reported
Duration of follow-up	48 weeks
Indirectness	None
Additional comments	ITT

Study arms

Moderate dose ICS/formoterol MART (N = 32)

160/4.5 mcg budesonide/formoterol, two inhalations twice daily plus additional inhalations as-needed for symptom relief

Regular moderate dose ICS/LABA inhaler (N = 31)

160/4.5 mcg budesonide/formoterol, two inhalations twice daily plus 100 mg salbutamol as-needed for symptom relief

Characteristics

Arm-level characteristics

Characteristic	Moderate dose ICS/formoterol MART (N = 32)	Regular moderate dose ICS/LABA inhaler (N = 31)
% Female	n = 19 ; % = 59	n = 21 ; % = 68

Characteristic	Moderate dose ICS/formoterol MART (N = 32)	Regular moderate dose ICS/LABA inhaler (N = 31)
Sample size		
Mean age (SD) Nominal	41	39
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose BDP equiv. Mean (SD)	574 (84)	610 (92)
Asthma control ACT score Mean (SD)	15.3 (2.2)	14.6 (3)
Lung function (% of predicted) FEV1 Mean (SD)	68.3 (8.7)	70.4 (10.2)

Outcomes

Study timepoints

- Baseline
- 48 week

Continuous Outcomes

Outcome	Moderate dose ICS/formoterol MART, Baseline, N = 32	Moderate dose ICS/formoterol MART, 48 week, N = NR	Regular moderate dose ICS/LABA inhaler, Baseline, N = 31	Regular moderate dose ICS/LABA inhaler, 48 week, N = NR
Reliever/rescue medication use (Inhalations per week) Final values Mean (SD)	11.2 (4)	3.6 (0.9)	10.6 (3.2)	5.6 (0.8)

Reliever/rescue medication use - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Moderate dose ICS/formoterol MART, Baseline, N = 32	Moderate dose ICS/formoterol MART, 48 week, N = NR	Regular moderate dose ICS/LABA inhaler, Baseline, N = 31	Regular moderate dose ICS/LABA inhaler, 48 week, N = NR
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 3 ; % = 9.7

Severe asthma exacerbations - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Reliever/rescuemedicationuse-MeanSD-Regular ICS/formoterol with ICS/formoterol prn -Regular moderate-high dose ICS inhaler-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, open label trial with no information on switching between study arms or additional medications given and no information given on dropout rates or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular ICS/formoterol with ICS/formoterol prn -Regular moderate-high dose ICS inhaler-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, open label trial with no information on switching between study arms or additional medications given and no information given on dropout rates or reasons for discontinuation)*
Overall bias and Directness	Overall Directness	Directly applicable

van Zyl-Smit, 2020

Bibliographic Reference	van Zyl-Smit, Richard N; Krull, Matthias; Gessner, Christian; Gon, Yasuhiro; Noga, Oliver; Richard, Alexia; de Los Reyes, Amy; Shu, Xu; Pethe, Abhijit; Tanase, Ana-Maria; D'Andrea, Peter; Once-daily mometasone plus indacaterol versus mometasone or twice-daily fluticasone plus salmeterol in patients with inadequately controlled asthma (PALLADIUM): a randomised, double-blind, triple-dummy, controlled phase 3 study.; The Lancet. Respiratory medicine; 2020; vol. 8 (no. 10); 987-999

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	PALLADIUM
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	No additional information
Study dates	December 2015 - May 2018
Sources of funding	Funded by Novartis
Inclusion criteria	Aged 12 to 75 years

	Diagnosis of asthma for at least 1 year Receiving moderate-dose or high-dose ICS monotherapy or low-dose ICS–LABA combination for asthma for at least 3 months and at stable doses for at least 1 month before screening ACQ-7 score of at least 1·5 at screening Qualifying for treatment with moderate-dose or high-dose ICS–LABA FEV1 of 50–85% of predicted FEV1 increase of at least 12% and 200 mL after receiving SABA
Exclusion criteria	Asthma attack or exacerbation requiring systemic steroids, hospitalisation, or emergency room visit within 6 weeks History of chronic lung disease including COPD Smoking within 6 months before screening, or had a >10 pack-year smoking history Previously intubated for asthma
Recruitment / selection of participants	Recruited from 316 centres, method not reported
Intervention(s)	Following a 2-week screening period and a 2-week run-in period where participants received low-dose ICS, those randomised to the ICS/LABA arm received either 500/50 mcg fluticasone propionate/salmeterol, one inhalation twice per day via Diskus inhaler, or 320/150 mometasone furoate/indacaterol, once daily, plus placebo inhalers. Salbutamol was available to be used as-needed for symptom relief throughout.

	Study also included an arm containing low-dose mometasone furoate/indacaterol combination inhalers (160/150 mcg per day) excluded from this review due to being a low-dose ICS/LABA combination
Population subgroups	**Exacerbations** Mixed - 69% none, 24% one, 7% more than one in the past year **Atopy** Not reported
Comparator	Following a 2-week screening period and a 2-week run-in period where participants received low-dose ICS, those randomised to the ICS arm received 400 mcg mometasone furoate, one inhalation twice per day via Twisthaler, plus placebos via Diskus and Breezhaler. Salbutamol was available to be used as-needed for symptom relief throughout. *Study also included an arm containing 400 mcg mometasone furoate, one inhalation once per day, excluded from this review due to containing low-dose ICS monotherapy - not a relevant intervention*
Number of participants	2216 randomised 891 allocated to ICS/LABA, 799 completed 442 allocated to ICS, 394 completed 439 allocated to low-dose ICS/LABA (excluded from this review) 444 allocated to low-dose ICS (excluded from this review)
Duration of follow-up	52 weeks

Indirectness	None
Additional comments	ITT

Study arms

Regular moderate dose ICS (N = 442)
400 mcg mometasone furoate, one inhalation twice daily

Regular moderate/high dose ICS/LABA (N = 891)
500/50 mcg fluticasone propionate/salmeterol, one inhalation twice daily, or 320/150 mometasone furoate/indacaterol once daily *Two study arms combined for this review*

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS (N = 442)	Regular moderate/high dose ICS/LABA (N = 891)
% Female Sample size	n = 250 ; % = 57	n = 256 ; % = 57
Mean age (SD) Mean (SD)	47.5 (14.8)	48.9 (14.6)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Characteristic	Regular moderate dose ICS (N = 442)	Regular moderate/high dose ICS/LABA (N = 891)
ICS dose Sample size	n = NA ; % = NA	n = NA ; % = NA
Low-dose ICS Sample size	n = 1 ; % = 0	n = 4 ; % = 1
Moderate-dose ICS Sample size	n = 96 ; % = 22	n = 92 ; % = 21
High-dose ICS Sample size	n = 34 ; % = 8	n = 31 ; % = 7
Low-dose ICS/LABA Sample size	n = 299 ; % = 68	n = 302 ; % = 68
ICS/LABA other than low-dose Sample size	n = 8 ; % = 2	n = 15 ; % = 3
Asthma control ACQ-7 score Mean (SD)	2.3 (0.5)	2.3 (0.5)
Lung function (% of predicted) FEV1 Mean (SD)	67.6 (8.7)	66.8 (9)

Outcomes

Study timepoints

- Baseline
- 52 week

Dichotomous Outcomes

Outcome	Regular moderate dose ICS, Baseline, N = 442	Regular moderate dose ICS, 52 week, N = 442	Regular moderate/high dose ICS/LABA, Baseline, N = 891	Regular moderate/high dose ICS/LABA, 52 week, N = 891
Pneumonia Final values No of events	n = NA ; % = NA	n = 5 ; % = 1	n = NA ; % = NA	n = 1 ; % = 0
Mortality Final outcomes No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 308 ; % = 70	n = NA ; % = NA	n = 576 ; % = 65

Pneumonia - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Pneumonia-NoOfEvents-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored and 11% dropout rate with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored and 11% dropout rate with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Adherence not monitored and 11% dropout rate with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Virchow, 2019

Bibliographic Reference	Virchow, Johann Christian; Kuna, Piotr; Paggiaro, Pierluigi; Papi, Alberto; Singh, Dave; Corre, Sandrine; Zuccaro, Florence; Vele, Andrea; Kots, Maxim; Georges, George; Petruzzelli, Stefano; Canonica, Giorgio Walter; Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials.; Lancet (London, England); 2019; vol. 394 (no. 10210); 1737-1749

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	TRIMARAN and TRIGGER (only results of TRIMARAN shown in this review due to TRIGGER containing interventions that are not relevant to this review protocol)
Study type	Randomised controlled trial (RCT)
Study location	International
Study setting	Secondary and tertiary care centres and specialised investigation units
Study dates	February 2016 - May 2018
Sources of funding	Funded by Chiesi Farmaceutici
Inclusion criteria	Aged 18-75 years Diagnosed with asthma before age 40 and for ≥1 year

	FEV1 <80% of predicted and >12% and 200 mL reversibility after receiving SABA ACQ score ≥1.5 ≥1 exacerbation requiring systemic corticosteroids, emergency department visit or hospitalisation in the past year Receiving a stable moderate-dose of ICS plus a LABA for ≥4 weeks prior to screening
Exclusion criteria	History of near-fatal asthma or previous admission to intensive care unit for asthma Severe asthma exacerbation within 4 weeks or during the run-in period Any other substantial lung disease that could interfere with study assessments Current or former smokers with a history >10 pack years, or stopped smoking <1 year prior to study entry Receiving monoclonal antibodies or other biological drugs Significant cardiovascular conditions or laboratory abnormalities Unstable concurrent disease
Recruitment / selection of participants	No additional information

Intervention(s)	Following a 2-week run-in period where participants received 100/6 mcg beclomethasone dipropionate/formoterol fumarate, two inhalations twice per day, those randomised to the ICS/LABA arm continued to receive the same treatment as the run-in period. Salbutamol was provided throughout to be used as-needed.
Population subgroups	**Exacerbations** Yes - inclusion criteria **Atopy** Not reported
Comparator	Following a 2-week run-in period where participants received 100/6 mcg beclomethasone dipropionate/formoterol fumarate, two inhalations twice per day, those randomised to the ICS/LABA plus LAMA arm received 100/6/10 mcg beclomethasone dipropionate/formoterol fumarate/glycopyrronium, two inhalations twice per day. Salbutamol was provided throughout to be used as-needed.
Number of participants	1155 randomised 576 received ICS/LABA, 539 completed 579 received ICS/LABA + LAMA, 542 completed
Duration of follow-up	52 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular moderate dose ICS/LABA plus LAMA (N = 576)

100/6/10 mcg beclomethasone dipropionate/formoterol/glycopyrronium, two inhalations twice daily

Regular moderate dose ICS/LABA (N = 574)
100/6 mcg beclomethasone dipropionate/formoterol, two inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA plus LAMA (N = 576)	Regular moderate dose ICS/LABA (N = 574)
% Female Sample size	n = 353 ; % = 61	n = 355 ; % = 62
Mean age (SD) Mean (SD)	52.5 (12.2)	52.6 (12.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Asian Sample size	n = 0 ; % = 0	n = 0 ; % = 0
White Sample size	n = 574 ; % = 100	n = 575 ; % = 100
Other Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Comorbidities Nominal	NR	NR

Characteristic	Regular moderate dose ICS/LABA plus LAMA (N = 576)	Regular moderate dose ICS/LABA (N = 574)
ICS dose Sample size	n = NA ; % = NA	n = NA ; % = NA
ICS Sample size	n = 72 ; % = 13	n = 61 ; % = 11
ICS/LABA Sample size	n = 515 ; % = 90	n = 531 ; % = 92
LABA Sample size	n = 66 ; % = 11	n = 55 ; % = 10
Asthma control ACQ score Mean (SD)	2.3 (0.53)	2.3 (0.52)
Lung function (% of predicted) FEV1 Mean (SD)	55.7 (12)	55.2 (12.3)

Outcomes

Study timepoints

- Baseline
- 26 week
- 52 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA plus LAMA, Baseline, N = 576	Regular moderate dose ICS/LABA plus LAMA, 26 week, N = 575	Regular moderate dose ICS/LABA plus LAMA, 52 week, N = NA	Regular moderate dose ICS/LABA, Baseline, N = 574	Regular moderate dose ICS/LABA, 26 week, N = 574	Regular moderate dose ICS/LABA, 52 week, N = NA
Lung Function (FEV1) (ml) Change scores Mean (SD)	NA (NA)	127 (361)	NA (NA)	NA (NA)	185 (361)	NA (NA)
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	-3.1 (41.6)	NA (NA)	NA (NA)	5.3 (41.6)	NA (NA)

Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA plus LAMA, Baseline, N = 576	Regular moderate dose ICS/LABA plus LAMA, 26 week, N = NA	Regular moderate dose ICS/LABA plus LAMA, 52 week, N = 576	Regular moderate dose ICS/LABA, Baseline, N = 574	Regular moderate dose ICS/LABA, 26 week, N = NA	Regular moderate dose ICS/LABA, 52 week, N = 574
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = NA ; % = NA	n = 7 ; % = 1	n = NA ; % = NA	n = NA ; % = NA	n = 4 ; % = 1

Outcome	Regular moderate dose ICS/LABA plus LAMA, Baseline, N = 576	Regular moderate dose ICS/LABA plus LAMA, 26 week, N = NA	Regular moderate dose ICS/LABA plus LAMA, 52 week, N = 576	Regular moderate dose ICS/LABA, Baseline, N = 574	Regular moderate dose ICS/LABA, 26 week, N = NA	Regular moderate dose ICS/LABA, 52 week, N = 574
Mortality Final values No of events	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = NA ; % = NA	n = 3 ; % = 1
Pneumonia Final values No of events	n = NA ; % = NA	n = NA ; % = NA	n = 3 ; % = 1	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = NA ; % = NA	n = 455 ; % = 79	n = NA ; % = NA	n = NA ; % = NA	n = 431 ; % = 75

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Pneumonia - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Contrast Outcomes

Outcome	Regular moderate dose ICS/LABA plus LAMA vs Regular moderate dose ICS/LABA, Baseline, N2 = 574, N1 = 575	Regular moderate dose ICS/LABA plus LAMA vs Regular moderate dose ICS/LABA, 26 week, N2 = NA, N1 = NA	Regular moderate dose ICS/LABA plus LAMA vs Regular moderate dose ICS/LABA, 52 week, N2 = 574, N1 = 575
Time to first exacerbation Hazard ratio/95% CI	NA (NA to NA)	NR (NR to NR)	0.84 (0.73 to 0.98)

Time to first moderate or severe exacerbation

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular low-moderate dose ICS/LABA plus LAMA-Regular moderate-high dose ICS/LABA-t26

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Treatment adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(PEF)-MeanSD-Regular low-moderate dose ICS/LABA plus LAMA-Regular moderate-high dose ICS/LABA-t26

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Treatment adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular low-moderate dose ICS/LABA plus LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Treatment adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular low-moderate dose ICS/LABA plus LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Treatment adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia-NoOfEvents-Regular low-moderate dose ICS/LABA plus LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Treatment adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular low-moderate dose ICS/LABA plus LAMA-Regular moderate-high dose ICS/LABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Treatment adherence not monitored)*
Overall bias and Directness	Overall Directness	Directly applicable

Vogelmeier, 2005

Bibliographic Reference	Vogelmeier, C; D'Urzo, A; Pauwels, R; Merino, J M; Jaspal, M; Boutet, S; Naya, I; Price, D; Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option?.; The European respiratory journal; 2005; vol. 26 (no. 5); 819-28

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Multicentre, international
Study setting	246 centres in 16 countries
Study dates	No additional information
Sources of funding	Supported by AstraZeneca
Inclusion criteria	Aged ≥12 years Diagnosis of asthma (as defined by the American Thoracic Society for ≥6 months

	Receiving ≥500 mcg budesonide, fluticasone, or ≥1000 mcg of any other ICS per day for at least once month prior to the study Pre-treatment FEV1 40-90% of predicted ≥1 severe exacerbation within 12 months of study entry Used as-needed medication on ≥4 of the last 7 days of the run-in
Exclusion criteria	Receiving an ICS/LABA inhaler (budesonide/formoterol or salmeterol/fluticason) in the previous 3 months
Recruitment / selection of participants	Participants recruited from 246 centres in 16 countries, method not reported
Intervention(s)	Following a two-week run-in period where participants received their usual ICS with as-needed medication, those randomised to the regular ICS/LABA plus as-needed ICS/LABA arm received 160/4.5 mcg budesonide/formoterol, two inhalations twice daily, plus additional inhalations as-needed for symptom relief. After four weeks the dose of budesonide/formoterol could have been down-titrated from four-times daily to twice daily at the treating clinicians discretion.
Population subgroups	<u>Exacerbations</u> Yes - all participants had at least one exacerbation in the past year <u>Atopy</u> Not reported
Comparator	Following a two-week run-in period where participants received their usual ICS with as-needed medication, those randomised to the ICS/LABA arm received 50/250 mcg salmeterol/fluticasone, one inhalation twice daily, plus salbutamol as-needed for symptom relief (as rescue medication, via dru powder inhaler). After four weeks the dose of

	salmeterol/fluticasone could have been down-titrated from 50/250 mcg twice daily to 50/100 mcg twice daily, at the treating clinicians discretion.
Number of participants	2143 randomised 1067 received regular ICS/formoterol plus as-needed, 948 completed 1076 received regular ICS/LABA, 926 completed
Duration of follow-up	52 weeks
Indirectness	Intervention indirectness due to the down-titration of ICS/LABA from moderate to low-dose, where deemed appropriate
Additional comments	Intention to treat

Study arms

Moderate dose ICS/formoterol MART (N = 1067)

160/4.5 mcg budesonide/formoterol, two inhalations twice daily, plus additional inhalations as-needed for symptom relief

Regular moderate dose ICS/LABA plus as needed SABA (N = 1076)

50/250 mcg salmeterol/fluticasone, twice daily plus as needed salbutamol

Characteristics

Arm-level characteristics

Characteristic	Moderate dose ICS/formoterol MART (N = 1067)	Regular moderate dose ICS/LABA plus as needed SABA (N = 1076)
% Female Sample size	n = 616 ; % = 58	n = 647 ; % = 60

Characteristic	Moderate dose ICS/formoterol MART (N = 1067)	Regular moderate dose ICS/LABA plus as needed SABA (N = 1076)
Mean age (SD) Mean (range) Nominal	45	45
Mean age (SD) Mean (range) Range	12 to 80	12 to 84
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Mean (range) Nominal	888	881
ICS dose Mean (range) Range	50 to 2000	400 to 3000
Asthma control Mean (range) ACQ score Nominal	1.86	1.87

Characteristic	Moderate dose ICS/formoterol MART (N = 1067)	Regular moderate dose ICS/LABA plus as needed SABA (N = 1076)
Asthma control Mean (range) ACQ score Range	0 to 5.2	0 to 5
Lung function (% of predicted) Mean (range) FEV1 Nominal	73	73
Lung function (% of predicted) Mean (range) FEV1 Range	39 to 115	28 to 100

Outcomes

Study timepoints

- Baseline
- 52 week

Dichotomous Outcomes

Outcome	Moderate dose ICS/formoterol MART, Baseline, N = 1067	Moderate dose ICS/formoterol MART, 52 week, N = 1067	Regular moderate dose ICS/LABA plus as needed SABA, Baseline, N = 1076	Regular moderate dose ICS/LABA plus as needed SABA, 52 week, N = 1076
Severe asthma exacerbations	n = NA ; % = NA	n = 159 ; % = 15	n = NA ; % = NA	n = 204 ; % = 19

Outcome	Moderate dose ICS/formoterol MART, Baseline, N = 1067	Moderate dose ICS/formoterol MART, 52 week, N = 1067	Regular moderate dose ICS/LABA plus as needed SABA, Baseline, N = 1076	Regular moderate dose ICS/LABA plus as needed SABA, 52 week, N = 1076
Number of participants with at least one event No of events				
Mortality No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 2 ; % = 0
Adverse events No of events	n = NA ; % = NA	n = 80 ; % = 7.5	n = NA ; % = NA	n = 88 ; % = 8.2
Rescue/reliever medication use (>4 inhalations/week) No of events	n = NA ; % = NA	n = 811 ; % = 76	n = NA ; % = NA	n = 710 ; % = 66

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Rescue/reliever medication use (>4 inhalations/week) - Polarity - Lower values are better

Contrast Outcomes

Outcome	Moderate dose ICS/formoterol MART vs Regular moderate dose ICS/LABA plus as needed SABA, Baseline, N2 = 1076, N1 = 1067	Moderate dose ICS/formoterol MART vs Regular moderate dose ICS/LABA plus as needed SABA, 52 week, N2 = 1076, N1 = 1067
Reliever/rescue medication use (Puffs per day) Final values Mean (p value)	NA (NA)	-0.35 (0.001)
Quality of life (Asthma quality of life questionnaire with standard activities) Scale range: 1-7, change scores Mean (p value)	NA (NA)	0.03 (0.51)
Asthma control (Asthma Control Questionnaire) Scale range: 1-6, change scores Mean (p value)	NA (NA)	-0.06 (0.069)
Lung Function (FEV1) (Litres) Change scores Mean (p value)	NA (NA)	0.03 (0.066)

Reliever/rescue medication use - Polarity - Lower values are better
Quality of life (Asthma quality of life questionnaire with standard activities) - Polarity - Higher values are better
Asthma control (Asthma Control Questionnaire) - Polarity - Lower values are better
Lung Function (FEV1) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA plus as-needed ICS/LABA-Regular moderate-high dose ICS/LABA plus as-needed SABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(up/down titration allowed at week 4 onwards plus addition of other asthma controller medication was allowed and study was open-label; deviation from inclusion criteria (inclusion of people with higher and lower FEV1 than pre-scpecified); selective reporting of dichotomous data: time-to-event data variance not reported)*
Overall bias and Directness	Overall Directness	Partially applicable *(Potentially indirect comparison: starting on moderate ICS but then down titration allowed so participants could end up on low-dose ICS which is not relevant to the review protocol)*

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA plus as-needed ICS/LABA-Regular moderate-high dose ICS/LABA plus as-needed SABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(up/down titration allowed at week 4 onwards plus addition of other asthma controller medication was allowed and study was open-label; deviation from inclusion criteria (inclusion of people with higher and lower FEV1 than pre-specified))*
Overall bias and Directness	Overall Directness	Partially applicable *(Potentially indirect comparison: starting on moderate ICS but then down titration allowed so participants could end up on low-dose ICS which is not relevant to the review protocol)*

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA plus as-needed ICS/LABA-Regular moderate-high dose ICS/LABA plus as-needed SABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(up/down titration allowed at week 4 onwards plus addition of other asthma controller medication was allowed*

Section	Question	Answer
		and study was open-label; deviation from inclusion criteria (inclusion of people with higher and lower FEV1 than pre-specified))
Overall bias and Directness	Overall Directness	Partially applicable *(Potentially indirect comparison: starting on moderate ICS but then down titration allowed so participants could end up on low-dose ICS which is not relevant to the review protocol)*

ContrastOutcomes-Reliever/rescuemedicationuse-MeanPValue-Regular moderate-high dose ICS/LABA plus as-needed ICS/LABA-Regular moderate-high dose ICS/LABA plus as-needed SABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(up/down titration allowed at week 4 onwards plus addition of other asthma controller medication was allowed and study was open-label; deviation from inclusion criteria (inclusion of people with higher and lower FEV1 than pre-scpecified); selective reporting of dichotomous data: time-to-event data variance not reported)*
Overall bias and Directness	Overall Directness	Partially applicable *(Potentially indirect comparison: starting on moderate ICS but then down titration allowed so participants could end up on low-dose ICS which is not relevant to the review protocol)*

ContrastOutcomes-Qualityoflife(Asthmaqualityoflifequestionnairewithstandardactivities)-MeanPValue-Regular moderate-high dose ICS/LABA plus as-needed ICS/LABA-Regular moderate-high dose ICS/LABA plus as-needed SABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(up/down titration allowed at week 4 onwards plus addition of other asthma controller medication was allowed and study was open-label; deviation from inclusion criteria (inclusion of people with higher and lower FEV1 than pre-scpecified); selective reporting of dichotomous data: time-to-event data variance not reported)*
Overall bias and Directness	Overall Directness	Partially applicable *(Potentially indirect comparison: starting on moderate ICS but then down titration allowed so participants could end up on low-dose ICS which is not relevant to the review protocol)*

ContrastOutcomes-Asthmacontrol(AsthmaControlQuestionnaire)-MeanPValue-Regular moderate-high dose ICS/LABA plus as-needed ICS/LABA-Regular moderate-high dose ICS/LABA plus as-needed SABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(up/down titration allowed at week 4 onwards plus addition of other asthma controller medication was allowed and study was open-label; deviation from inclusion criteria (inclusion of people with higher and lower FEV1 than pre-scpecified); selective reporting of dichotomous data: time-to-event data variance not reported)*
Overall bias and Directness	Overall Directness	Partially applicable *(Potentially indirect comparison: starting on moderate ICS but then down titration allowed so participants could end up on low-dose ICS which is not relevant to the review protocol)*

ContrastOutcomes-LungFunction(FEV1)-MeanPValue-Regular moderate-high dose ICS/LABA plus as-needed ICS/LABA-Regular moderate-high dose ICS/LABA plus as-needed SABA-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(up/down titration allowed at week 4 onwards plus addition of other asthma controller medication was allowed and study was open-label; deviation from inclusion criteria (inclusion of people with higher and lower FEV1 than pre-scpecified); selective reporting of dichotomous data: time-to-event data variance not reported)*
Overall bias and Directness	Overall Directness	Partially applicable *(Potentially indirect comparison: starting on moderate ICS but then down titration allowed so participants could end up on low-dose ICS which is not relevant to the review protocol)*

Wallin, 2003

Bibliographic Reference	Wallin, Annika; Sue-Chu, Malcolm; Bjermer, Leif; Ward, Jonathan; Sandstrom, Thomas; Lindberg, Anne; Lundback, Bo; Djukanovic, Ratko; Holgate, Stephen; Wilson, Susan; Effect of inhaled fluticasone with and without salmeterol on airway inflammation in asthma.; The Journal of allergy and clinical immunology; 2003; vol. 112 (no. 1); 72-8

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Norway
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by Glaxo Wellcome
Inclusion criteria	Free of respiratory tract infections within 4 weeks

	Clinical need for extension of treatment on the basis of both symptoms (≥6 days, ≥4 nights with symptoms or SABA use) and pulmonary function (PEFv >20% on ≥4 days, ≥15% FEV1 or PEF reversibility after receiving SABA, PC20 methacholine <4 mg/mL) during the last 2 weeks of the run-in Receiving 800-1200 mcg budesonide or 400-500 mcg fluticasone propionate per day
Exclusion criteria	None reported
Recruitment / selection of participants	No additional information
Intervention(s)	Following a 2-4-week run-in period, participants allocated to the ICS/LABA arm received 200 mcg fluticasone propionate along with 50 mcg salmeterol, each taken as one inhalation twice per day via Diskus/Accuhaler inhalers. Participants were also provided with Salbutamol to be used as-needed for symptom relief.
Population subgroups	**Exacerbations** Not reported **Atopy** Mixed - 22/37 participants with positive skin prick test
Comparator	Following a 2-4-week run-in period, participants allocated to the ICS arm received 500 mcg fluticasone propionate, taken as one inhalation twice per day via Diskus inhaler, with salbutamol used as-needed for symptom relief. *Study also included an arm containing 200 mcg fluticasone propionate taken twice daily, not included in this review due to being low-dose ICS monotherapy - not a relevant intervention in this review*
Number of participants	56 randomised

	18 allocated to ICS/LABA, 14 completed 19 allocated to moderate-high dose ICS, 16 completed 19 allocated to low-dose ICS (excluded from this review)
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	Available case analysis

Study arms

Regular high dose ICS (N = 19)

500 mcg fluticasone propionate, one inhalation twice per day

Regular moderate dose ICS/LABA (N = 18)

200 mcg fluticasone propionate plus 50 mcg salmeterol, one inhalation twice per day

Characteristics

Arm-level characteristics

Characteristic	Regular high dose ICS (N = 19)	Regular moderate dose ICS/LABA (N = 18)
% Female Sample size	n = 10 ; % = 53	n = 7 ; % = 39
Mean age (SD) Mean (SD)	40 (15)	43 (16)

Characteristic	Regular high dose ICS (N = 19)	Regular moderate dose ICS/LABA (N = 18)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	92 (12)	80 (16)

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous Outcomes

Outcome	Regular high dose ICS, Baseline, N = 19	Regular high dose ICS, 12 week, N = 19	Regular moderate dose ICS/LABA, Baseline, N = 18	Regular moderate dose ICS/LABA, 12 week, N = 18
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 2 ; % = 10	n = NA ; % = NA	n = 1 ; % = 6

Severe asthma exacerbations - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS-Regular moderate-high dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, analysis method not specified, no adherence monitoring included and 19% dropout rate with discontinuation reasons related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Wang, 2015

Bibliographic Reference	Wang, K; Tian, P; Fan, Y; Wang, Y; Liu, C; Assessment of second-line treatments for patients with uncontrolled moderate asthma; International journal of clinical and experimental medicine; 2015; vol. 8 (no. 10); 19476-19480

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	No additional information
Study dates	No additional information
Sources of funding	None reported
Inclusion criteria	Moderate asthma Daily symptoms Exacerbations affecting daily activity and sleep

	Nocturnal symptoms more than once per week Daily use of SABA FEV1 or PEF 60-80% of predicted FEV1 or PEF variability >30% ACT score between 12 and 20
Exclusion criteria	None reported
Recruitment / selection of participants	No additional information
Intervention(s)	Eligible participants received 50/250 mcg salmeterol/fluticasone propionate for a 3 month minimum run-in period, after which they were allocated to one of three interventions: • 50/250 mcg salmeterol/fluticasone propionate twice daily plus 18 mcg tiotropium once daily • 50/250 mcg salmeterol/fluticasone propionate twice daily plus 10 mg montelukast once daily • 50/500 mcg salmeterol/fluticasone propionate twice daily
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported

Comparator	See interventions
Number of participants	94 randomised 33 allocated to ICS/LABA+LAMA 31 allocated to ICS/LABA+montelukast 30 allocated to ICS/LABA
Duration of follow-up	16 weeks
Indirectness	None
Additional comments	Available case analysis. All baseline characteristics and outcomes reported by study as standard error of the mean - deemed to be a reporting error by the technical analyst and therefore taken as standard deviation

Study arms

Regular moderate dose ICS/LABA plus LAMA (N = 33)
50/250 mcg salmeterol/fluticasone propionate twice daily plus 18 mcg tiotropium once per day

Regular moderate dose ICS/LABA plus montelukast (N = 31)
50/250 mcg salmeterol/fluticasone propionate twice daily plus 10 mg montelukast once per day

Regular moderate dose ICS/LABA (N = 30)
50/500 mcg salmeterol/fluticasone propionate twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA plus LAMA (N = 33)	Regular moderate dose ICS/LABA plus montelukast (N = 31)	Regular moderate dose ICS/LABA (N = 30)
% Female Sample size	n = 15 ; % = 45	n = 15 ; % = 48	n = 14 ; % = 47
Mean age (SD) Mean (SD)	36.7 (5.8)	37.2 (6.1)	35.3 (5.9)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
ICS dose Nominal	NR	NR	NR
Asthma control ACT score Mean (SD)	18.67 (1.73)	18.38 (1.19)	18.5 (1.6)
Lung function (%) PEF variability Mean (SD)	26.22 (6.38)	23.25 (4.92)	24.38 (4.77)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA plus LAMA, Baseline, N = 33	Regular moderate dose ICS/LABA plus LAMA, 12 week, N = 33	Regular moderate dose ICS/LABA plus montelukast, Baseline, N = 31	Regular moderate dose ICS/LABA plus montelukast, 12 week, N = 31	Regular moderate dose ICS/LABA, Baseline, N = 30	Regular moderate dose ICS/LABA, 12 week, N = 30
Asthma Control (Asthma Control Test) Final values, scale range: 5-25 Mean (SD)	18.67 (1.73)	24.44 (1.01)	18.38 (1.19)	23.5 (0.53)	18.5 (1.6)	24.88 (0.35)
Inflammatory markers (FeNO) (ppb) Final values Mean (SD)	58.11 (24.76)	30.01 (12.46)	55.63 (16.81)	21.13 (7.98)	64.38 (28.6)	14.38 (5.83)

Asthma Control (Asthma Control Test) - Polarity - Higher values are better
Inflammatory markers (FeNO) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-AsthmaControl(AsthmaControlTest)-MeanSD-Regular low-moderate dose ICS/LABA plus LAMA-Regular low-moderate dose ICS/LABA plus montelukast-Regular moderate-high dose ICS/LABA-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, method of analysis not reported and no information on switching between groups, additional medications given or adherence to study therapies and subjective outcome measure with knowledge of intervention received)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Inflammatorymarkers(FeNO)-MeanSD-Regular low-moderate dose ICS/LABA plus LAMA-Regular low-moderate dose ICS/LABA plus montelukast-Regular moderate-high dose ICS/LABA-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, method of analysis not reported and no information on switching between groups, additional medications given or adherence to study therapies)*
Overall bias and Directness	Overall Directness	Directly applicable

Ye, 2015

Bibliographic Reference	Ye, Young Min; Kim, Sang Ha; Hur, Gyu Young; Kim, Joo Hee; Park, Jung Won; Shim, Jae Jeong; Jung, Ki Suck; Lee, Hyun Young; Park, Hae Sim; Addition of Montelukast to Low-Dose Inhaled Corticosteroid Leads to Fewer Exacerbations in Older Patients Than Moderate-Dose Inhaled Corticosteroid Monotherapy.; Allergy, asthma & immunology research; 2015; vol. 7 (no. 5); 440-8

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT 01147510
Study type	Randomised controlled trial (RCT)
Study location	Korea
Study setting	Multicentre, 5 University hospitals in Korea
Study dates	Recruitment between August 2011 and February 2012; 12 week treatment period for each patient with last patient completing the study on July 28, 2012
Sources of funding	Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI14C1061), and partly supported by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp.
Inclusion criteria	Outpatients aged 60-75 years, who had been diagnosed with asthma more than 6 months before enrolment in the study based on clinical symptoms (such as cough, wheezing, breathlessness, chest tightness and dyspnoea), airway reversibility

	(defined by an increase of forced expiratory volume in one second (FEV1) >12% and 200 mL from pre-bronchodilator use), and airway hyperresponsiveness (PC20 <16 mg/mL of methacholine); currently being treated with ICS (budesonide 400 µg/day or equivalent) or a combination of low-dose inhaled budesonide and LABA (Seretide 250 µg/day or equivalent) for over 1 month before participating in this study; required to have normal results on complete blood count, routine chemistry, urinalysis and electrocardiogram at screening. After a 4-week run-in period, people not meeting criteria of GINA-defined 'well controlled asthma' (day symptoms of twice or less in a week, no limit of activities, no night symptom and sleep disturbance, use of reliever of twice or less in a week, normal FEV1 (over 80% predicted value), and no exacerbation) were randomised.
Exclusion criteria	Patients were excluded if they (1) had other acute diseases within 28 days before administration of trial medications, (2) had history of hypersensitivity to montelukast or budesonide, (3) were either current or former smokers with a smoking history of more than 10 pack years, and (4) required administration of any medications that may affect asthma control, such as systemic steroids and immunomodulatory drugs (cyclosporine, omalizumab, etc.) due to diseases other than asthma.
Recruitment / selection of participants	Method not specified; people meeting inclusion criteria.
Intervention(s)	inhaled budesonide 400 µg per day plus 10mg of montelukast for 12 weeks
Comparator	inhaled budesonide 800 µg per day for 12 weeks
Number of participants	157 patients screened, 140 randomised to treatment groups and 12 withdrawn after randomisation.
Duration of follow-up	12 weeks
Indirectness	none
Additional comments	Multivariate ordinal regression analysis with reference to the uncontrolled group was applied to determine predictors of asthma control status over the 12 weeks of treatment. In all analyses, P<0.05 was taken to indicate statistical significance. To evaluate the difference in proportions of subjects with ACT scores at the end of treatment ≥20 between the 2 treatment groups, the proportion test using by R 3.0.2 was performed.21 The correlations between changes in ACT and other clinical assessments, including FEV1, PFS and GDS, were analyzed by Spearman’s Rho test. Pearson’s chi-square test was used

	for comparing gender among the patients with 3 levels of asthma control at the end of the study. ANOVA was used for comparing baseline BMI and changes from baseline in clinical parameters, such as lung function and ACT.

Study arms

Regular low dose ICS plus Montelukast (N = 70)
400 µg budesonide per day plus 10mg of montelukast

Regular moderate dose ICS (N = 70)
800 µg budesonide per day

Characteristics

Arm-level characteristics

Characteristic	Regular low dose ICS plus Montelukast (N = 70)	Regular moderate dose ICS (N = 70)
% Female Sample size	n = 39 ; % = 55.7	n = 38 ; % = 54.3
Mean age (SD) Mean (SD)	68.2 (5.5)	67.3 (5.1)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR

Characteristic	Regular low dose ICS plus Montelukast (N = 70)	Regular moderate dose ICS (N = 70)
Asthma control ACT Score Mean (SD)	18.8 (4.6)	18.6 (4.6)
Lung function (% of predicted) FEV1 Mean (SD)	95.5 (26.5)	95.7 (21.3)

Outcomes

Study timepoints

- Baseline
- 12 week (Measures of pulmonary function test (PFT) and ACT were obtained at baseline and every 4 weeks during the treatment period.)

Continuous Outcomes

Outcome	Regular low dose ICS plus Montelukast, Baseline, N = 70	Regular low dose ICS plus Montelukast, 12 week, N = 70	Regular moderate dose ICS, Baseline, N = 70	Regular moderate dose ICS, 12 week, N = 70
Asthma control (ACT) Final values, scale range: 5-25 Mean (SD)	NA (NA)	19.4 (4.7)	NA (NA)	18.9 (4.6)
Lung Function (FEV1) (% of predicted) Change scores	NA (NA)	1.97 (10.72)	NA (NA)	-0.97 (9.1)

Outcome	Regular low dose ICS plus Montelukast, Baseline, N = 70	Regular low dose ICS plus Montelukast, 12 week, N = 70	Regular moderate dose ICS, Baseline, N = 70	Regular moderate dose ICS, 12 week, N = 70
Mean (SD)				
Severe exacerbation rate Total number of events, final values Nominal	NA	9	NA	20

Asthma control (ACT) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better
Severe exacerbation rate - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Regular low dose ICS plus Montelukast, Baseline, N = 70	Regular low dose ICS plus Montelukast, 12 week, N = 70	Regular moderate dose ICS, Baseline, N = 70	Regular moderate dose ICS, 12 week, N = 70
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 7 ; % = 10	n = NA ; % = NA	n = 12 ; % = 17

Severe asthma exacerbations - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Effectivenessoutcomes-ACT-MeanSD-regular low dose ICS + Montelukast-regular moderate dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Self-reported outcome and open-label study; unclear if missing data and/or if ITT or PP analyses used; no pre-specification of analyses in a protocol.)*
Overall bias and Directness	Overall Directness	Directly applicable

Effectivenessoutcomes-FEV1%predicted-MeanSD-regular low dose ICS + Montelukast-regular moderate dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unclear if missing data for this outcome; whether ITT or PP analyses done; could have been selected; no pre-specified analyses in a protocol)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-regular low dose ICS + Montelukast-regular moderate dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Self-reported outcome and open-label study; unclear if missing data and/or if ITT or PP analyses used; no pre-specification of analyses in a protocol.)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect timepoint: outcome assessed at 3 months, not meeting protocol specified time point of 6 months)*

ContinuousOutcomes-Severeexacerbationrate-Nominal-Regular low dose ICS plus Montelukast-Regular moderate dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Self-reported outcome and open-label study; unclear if missing data and/or if ITT or PP analyses used; no pre-specification of analyses in a protocol.)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect timepoint: outcome assessed at 3 months, not meeting protocol specified time point of 6 months)*

Zangrilli, 2011

Bibliographic Reference	Zangrilli, James; Mansfield, Lyndon E; Uryniak, Tom; O'Brien, Christopher D; Efficacy of budesonide/formoterol pressurized metered-dose inhaler versus budesonide pressurized metered-dose inhaler alone in Hispanic adults and adolescents with asthma: a randomized, controlled trial.; Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology; 2011; vol. 107 (no. 3); 258-65e2

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT 00419757
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by AstraZeneca
Inclusion criteria	Hispanic people aged ≥12 years Asthma diagnosis for ≥6 months

	Receiving moderate-high dose ICS alone or in combination with a LABA for ≥30 days FEV1 45-85% of predicted and reversibility ≥12% or 200 mL after receiving SABA Day or night time symptom scores >0 on ≥3 of 7 consecutive days during the run-in period
Exclusion criteria	Required hospitalisation once, or emergency treatment more than once in the previous 6 months Used systemic corticosteroids in the past month Smoking history >10 pack years
Recruitment / selection of participants	Recruited from 36 centres, method not reported
Intervention(s)	Following a 2-week run-in period where participants received 160 mcg budesonide, two inhalations twice daily, participants allocated to the ICS/LABA arm received 160/4.5 mcg budesonide/formoterol, two inhalations twice per day plus albuterol as-needed for symptom relief
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	Following a 2-week run-in period where participants received 160 mcg budesonide, two inhalations twice daily, participants allocated to the ICS arm received 160 mcg budesonide, two inhalations twice per day plus albuterol as-needed for symptom relief

Number of participants	250 randomised 127 allocated to ICS/LABA, 109 completed 123 allocated to ICS, 102 completed
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular moderate dose ICS/LABA (N = 127)

160/4.5 mcg budesonide/formoterol, two inhalations twice daily

Regular moderate dose ICS (N = 123)

160 mcg budesonide, two inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 127)	Regular moderate dose ICS (N = 123)
% Female Sample size	n = 84 ; % = 66	n = 80 ; % = 65
Mean age (SD) Mean (SD)	39.8 (16.6)	37 (14.9)

Characteristic	Regular moderate dose ICS/LABA (N = 127)	Regular moderate dose ICS (N = 123)
Ethnicity Self-reported descent Sample size	n = NA ; % = NA	n = NA ; % = NA
Mexican Sample size	n = 67 ; % = 53	n = 60 ; % = 49
Puerto Rican Sample size	n = 26 ; % = 21	n = 27 ; % = 22
Cuban Sample size	n = 17 ; % = 13	n = 16 ; % = 13
South or Central American Sample size	n = 13 ; % = 10	n = 18 ; % = 15
Caribbean Sample size	n = 2 ; % = 2	n = 1 ; % = 1
Mixed Hispanic Sample size	n = 2 ; % = 2	n = 1 ; % = 1
Comorbidities Nominal	NR	NR
ICS dose Range	80 to 2000	80 to 1600

Characteristic	Regular moderate dose ICS/LABA (N = 127)	Regular moderate dose ICS (N = 123)
ICS dose Mean (SD)	582.5 (282.4)	607 (294.5)
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Mean (SD)	68.3 (10.6)	68 (12.2)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 127	Regular moderate dose ICS/LABA, 12 week, N = 125	Regular moderate dose ICS, Baseline, N = 123	Regular moderate dose ICS, 12 week, N = 119
Reliever medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-0.7 (1.2)	NA (NA)	-0.6 (1.9)

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 127	Regular moderate dose ICS/LABA, 12 week, N = 125	Regular moderate dose ICS, Baseline, N = 123	Regular moderate dose ICS, 12 week, N = 119
Reliever medication use (SABA free days) (%) Change scores Mean (SD)	NA (NA)	17.6 (32.9)	NA (NA)	16.7 (33.5)

Reliever medication use - Polarity - Lower values are better
Reliever medication use (SABA free days) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 127	Regular moderate dose ICS/LABA, 12 week, N = 127	Regular moderate dose ICS, Baseline, N = 123	Regular moderate dose ICS, 12 week, N = 123
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 52 ; % = 40.9	n = NA ; % = NA	n = 46 ; % = 37.4

Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Relievermedicationuse-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 16% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Relievermedicationuse(SABAfreedays)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 16% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 16% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 16% dropout rate and reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Zetterstrom, 2001

Bibliographic Reference	Zetterstrom, O; Buhl, R; Mellem, H; Perpina, M; Hedman, J; O'Neill, S; Ekstrom, T; Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone.; The European respiratory journal; 2001; vol. 18 (no. 2); 262-8

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Multinational - Finland, Germany, Ireland, Norway, Spain and Sweden
Study setting	No additional information
Study dates	No additional information
Sources of funding	Supported by AstraZeneca
Inclusion criteria	Aged ≥18 years Receiving ICS at a constant daily dose ≥500 mcg for ≥30 days FEV1 50-90% of predicted and reversibility ≥15% after receiving SABA

Exclusion criteria	Use of systemic corticosteroids within 30 days Respiratory infection Seasonal asthma Severe cardiovascular disorder History of heavy smoking (≥10 pack years) Pregnant, or not using contraception if of childbearing potential
Recruitment / selection of participants	Recruited from 59 centres, method not reported
Intervention(s)	Following a 2-week run-in period where participants received their usual ICS therapy, those allocated to the ICS/LABA arm received one of two therapy regimens: • 160/4.5 mcg budesonide/formoterol, two inhalations twice per day via a single inhaler • 200 mcg budesonide plus 4.5 mcg formoterol, two inhalations of each twice per day via separate inhalers Participants also received terbutaline or salbutamol to be used as-needed for symptom relief *Two study arms containing combination and concurrent ICS/LABA administration combined for this review*
Population subgroups	**Exacerbations** Not reported

	Atopy Not reported
Comparator	Following a 2-week run-in period where participants received their usual ICS therapy, those allocated to the ICS arm received 200 mcg budesonide, two inhalations twice per day, plus terbutaline or salbutamol as-needed for symptom relief
Number of participants	362 randomised 123 received ICS/LABA 115 received ICS+LABA 124 received ICS
Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular moderate dose ICS/LABA (N = 238)
160/4.5 mcg budesonide formoterol in a single inhaler, or 200 mcg budesonide and 4.5 mcg formoterol, two inhalations twice per day
Two study arms containing combination and concurrent ICS/LABA combined for this review

Regular moderate dose ICS (N = 124)
200 mcg budesonide, two inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular moderate dose ICS/LABA (N = 238)	Regular moderate dose ICS (N = 124)
% Female Sample size	n = 113 ; % = 47	n = 62 ; % = 50
Mean age (SD) Nominal	45.7	48.5
Mean age (SD) Range	18 to 78	21 to 78
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
ICS dose Nominal	972	936
Asthma control Nominal	NR	NR
Lung function (% of predicted) FEV1 Nominal	74.1	73.1

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 238	Regular moderate dose ICS/LABA, 12 week, N = 238	Regular moderate dose ICS, Baseline, N = 124	Regular moderate dose ICS, 12 week, N = 124
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	33.91 (41.09)	NA (NA)	0.2 (41.8)
Reliever medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	-1.06 (2.51)	NA (NA)	-0.44 (1.73)
Reliever medication use (SABA-free days) (%) Change scores Mean (SD)	NA (NA)	31.9 (31.4)	NA (NA)	12.8 (32.1)
Lung Function (FEV1) (Litres) Final values Mean (SD)	2.3 (NR)	2.48 (0.42)	2.24 (NR)	2.35 (0.43)

Lung function (PEF) - Polarity - Higher values are better

Reliever medication use - Polarity - Lower values are better
Reliever medication use (SABA-free days) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular moderate dose ICS/LABA, Baseline, N = 238	Regular moderate dose ICS/LABA, 12 week, N = 238	Regular moderate dose ICS, Baseline, N = 124	Regular moderate dose ICS, 12 week, N = 124
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 19 ; % = 8	n = NA ; % = NA	n = 11 ; % = 9
Pneumonia (respiratory infections) Final values No of events	n = NA ; % = NA	n = 55 ; % = 23	n = NA ; % = NA	n = 32 ; % = 26

Severe asthma exacerbations - Polarity - Lower values are better
Pneumonia (respiratory infections) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT ContinuousOutcomes-Lungfunction(PEF)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(15% dropout rate with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Relievermedicationuse-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(15% dropout rate with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Relievermedicationuse(SABA-freedays)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(15% dropout rate with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(15% dropout rate with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(15% dropout rate with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia(respiratoryinfections)-NoOfEvents-Regular moderate-high dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(15% dropout rate with reasons for discontinuation related to participant's health status)*
Overall bias and Directness	Overall Directness	Indirectly applicable

D.3 Children aged 5-11 years

Berger, 2010

Bibliographic Reference	Berger, William E; Leflein, Jeffrey G; Geller, David E; Parasuraman, Bhash; Miller, Christopher J; O'Brien, Christopher D; O'Dowd, Liza; The safety and clinical benefit of budesonide/formoterol pressurized metered-dose inhaler versus budesonide alone in children.; Allergy and asthma proceedings; 2010; vol. 31 (no. 1); 26-39

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	Study code SD-039-0719; NCT 00646529
Study location	29 US clinical sites
Study setting	US clinical sites
Study dates	No additional information
Sources of funding	AstraZeneca
Inclusion criteria	Subjects aged 6 –11 years with a documented diagnosis of asthma for >=6 months, as defined by the American Thoracic Society were eligible to participate. Subjects were required to have received daily ICS treatment (as monotherapy or in combination with other controller medications) at any consistent dose for >=4 weeks before screening and to have a forced expiratory volume in 1 second (FEV1) of >=50% of predicted normal >=6 hours after the last dose of a short-acting beta 2-adrenergic agonist and >=24 hours after the last dose of a LABA. Eligible subjects also must have had a documented history of reversibility of >=12% in FEV1 or of >=15% in peak expiratory flow within 15–30 minutes after inhaling albuterol.

Exclusion criteria	Subjects that required treatment with systemic corticosteroids within 4 weeks before screening or during run-in. Subjects with a significant medical condition that might put them at risk, influence their ability to participate in the study, or influence study results also were to be excluded. Subjects with any malignancy (other than basal cell carcinoma) within the past 5 years, a clinically significant laboratory test abnormality, or a clinically significant abnormal electrocardiogram (ECG) also were excluded.
Recruitment / selection of participants	No additional information
Intervention(s)	Budesonide/formoterol (320/9ug) BID N=124 Budesonide/formoterol (320/9ug) pMDI (160/4.5ug x 2 inhalations) twice daily Concomitant Medications: Albuterol pMDI was provided as rescue medication throughout the study but was to be withheld for >=6 hours before scheduled spirometry. If the subject experienced uncontrolled asthma or increased symptoms after 2 weeks of randomized treatment, leukotriene receptor antagonists, inhaled nonsteroidal anti-inflammatory agents, methylxanthines, and alternative short-acting beta2-adrenergic agonists could be added to study therapy as deemed necessary by the investigator. Attempts to limit use of add-on medication were to be made as symptoms improved. Oral corticosteroid bursts were allowed for the treatment of asthma exacerbations. No ICS or LABA therapy other than study medication was permitted. If a subject required ICS or LABA treatment in addition to the study medication provided, the subject was withdrawn from the study.
Population subgroups	Exacerbations: treatment requiring systemic corticosteroids within 4 weeks before screening or during run-in was an exclusion criteria. Atopy: no additional information.

Comparator	Budesonide (400 ug) BID N=63 Budesonide DPI 400ug (200ug X 2 inhalations) twice daily Concomitant Medications: Albuterol pMDI was provided as rescue medication throughout the study but was to be withheld for >=6 hours before scheduled spirometry. If the subject experienced uncontrolled asthma or increased symptoms after 2 weeks of randomized treatment, leukotriene receptor antagonists, inhaled nonsteroidal anti-inflammatory agents, methylxanthines, and alternative short-acting beta2-adrenergic agonists could be added to study therapy as deemed necessary by the investigator. Attempts to limit use of add-on medication were to be made as symptoms improved. Oral corticosteroid bursts were allowed for the treatment of asthma exacerbations. No ICS or LABA therapy other than study medication was permitted. If a subject required ICS or LABA treatment in addition to the study medication provided, the subject was withdrawn from the study.
Number of participants	187
Duration of follow-up	26 weeks
Indirectness	Study allowed any dose ICS with/without other controller at baseline
Additional comments	The safety analysis and the analyses of spirometry, global assessments, and health care resource utilization variables included data from all randomized subjects who received at least one dose of study medication. Quality of life was assessed in all subjects aged >=7 years in the safety analysis set and their caregivers, consistent with the age range in which the instruments are validated. For urinary cortisol, data were log-transformed before analysis, and least squares mean differences between treatments and 95% confidence intervals (CIs) from this ANCOVA model were exponentiated and expressed as treatment ratios between the budesonide/formoterol pMDI and budesonide DPI groups.

Study arms

Regular paediatric high dose ICS/LABA with SABA prn (N = 124)

Budesonide/formoterol (320/9ug) pMDI (160/4.5ug x 2 inhalations) twice daily

Regular paediatric high dose ICS plus SABA prn (N = 63)
Budesonide DPI 400ug (200ug X 2 inhalations) twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular paediatric high dose ICS/LABA with SABA prn (N = 124)	Regular paediatric high dose ICS plus SABA prn (N = 63)
% Female Sample size	n = 44 ; % = 35.8	n = 23 ; % = 36.5
Mean age (SD) Mean (SD)	9 (1.6)	9 (1.6)
White Sample size	n = 109 ; % = 88.6	n = 58 ; % = 92.1
Black Sample size	n = 11 ; % = 8.9	n = 3 ; % = 4.8
Asian Sample size	n = 1 ; % = 0.8	n = 1 ; % = 1.6
Other Sample size	n = 2 ; % = 1.6	n = 1 ; % = 1.6
Time since asthma diagnosis (years)	6 (3)	6 (2.9)

Characteristic	Regular paediatric high dose ICS/LABA with SABA prn (N = 124)	Regular paediatric high dose ICS plus SABA prn (N = 63)
Mean (SD)		
ICS use at entry (users and ug/day) Sample size	n = 120 ; % = 97.6	n = 63 ; % = 100
ICS use at entry (users and ug/day) Mean (SD)	306 (214.1)	309 (212.6)
LABA use at entry Sample size	n = 21 ; % = 17.1	n = 13 ; % = 20.6
Rescue medication use Sample size	n = 113 ; % = 91.9	n = 59 ; % = 93.7
FEV1 % predicted Predose at randomisation visit Mean (SD)	84.01 (13.5)	82.9 (13.3)

Outcomes

Study timepoints

- Baseline
- 26 week

Dichotomous outcomes

Outcome	Regular paediatric high dose ICS/LABA with SABA prn, Baseline, N = 123	Regular paediatric high dose ICS/LABA with SABA prn, 26 week, N = 123	Regular paediatric high dose ICS plus SABA prn, Baseline, N = 63	Regular paediatric high dose ICS plus SABA prn, 26 week, N = 63
Adverse events Considered to be related to study medication No of events	n = NA ; % = NA	n = 6 ; % = 4.9	n = NA ; % = NA	n = 4 ; % = 6.3
Pneumonia No of events	n = NA ; % = NA	n = 1 ; % = 0.8	n = NA ; % = NA	n = 0 ; % = 0
Hospital admissions Urgent care visits due to asthma or breathing problems No of events	n = NA ; % = NA	n = 4 ; % = 3.3	n = NA ; % = NA	n = 7 ; % = 11.1

Adverse events - Polarity - Lower values are better
Pneumonia - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better

Continuous outcomes

Outcome	Regular paediatric high dose ICS/LABA with SABA prn, Baseline, N = 108	Regular paediatric high dose ICS/LABA with SABA prn, 26 week, N = 108	Regular paediatric high dose ICS plus SABA prn, Baseline, N = 55	Regular paediatric high dose ICS plus SABA prn, 26 week, N = 55
Quality of life (Pediatric asthma quality of life questionnaire with standardised activities)	NA (NA)	0.53 (0.83)	NA (NA)	0.36 (0.97)

Outcome	Regular paediatric high dose ICS/LABA with SABA prn, Baseline, N = 108	Regular paediatric high dose ICS/LABA with SABA prn, 26 week, N = 108	Regular paediatric high dose ICS plus SABA prn, Baseline, N = 55	Regular paediatric high dose ICS plus SABA prn, 26 week, N = 55
Change score. Measured in children aged >=7 years only Mean (SD)				

Quality of life (Pediatric asthma quality of life questionnaire with standardised activities) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Dichotomousoutcomes-Adverseevents-NoOfEvents-Budesonide/formoterol (320/9ug) BID-Budesonide (400 ug) BID-t26

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Open-label so knowledge by assessors could have affected assessment of outcome. No information about adherence to interventions. No protocol available to assess pre-specified analyses. Deviations from intervention possible (concomitant medications) but likely to be balanced across arms.)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Pneumonia-NoOfEvents-Budesonide/formoterol (320/9ug) BID-Budesonide (400 ug) BID-t26

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Open-label so knowledge by assessors could have affected assessment of outcome. No information about adherence to interventions. No protocol available to assess pre-specified analyses. Deviations from intervention possible (concomitant medications) but likely to be balanced across arms.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Urgentcarevisitsduetoasthmaorbreathingproblems-NoOfEvents-Budesonide/formoterol (320/9ug) BID-Budesonide (400 ug) BID-t26

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Open-label so knowledge by assessors could have affected assessment of outcome. No information about adherence to interventions. No protocol available to assess pre-specified analyses. Deviations from intervention possible (concomitant medications) but likely to be balanced across arms.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome related to, but not identical to 'hospital admissions')*

Continuousoutcomes-PAQLQ-s(Pediatricasthmaqualityoflifequestionnairewithstandardisedactivities)-MeanSD-Budesonide/formoterol (320/9ug) BID-Budesonide (400 ug) BID-t26

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Open-label so knowledge by assessors could have affected assessment of outcome. No information about adherence to interventions. No protocol available to assess pre-specified analyses. Deviations from intervention possible (concomitant medications) but likely to be balanced across arms.)*
Overall bias and Directness	Overall Directness	Directly applicable

Bisgaard, 2006

Bibliographic Reference	Bisgaard, Hans; Le Roux, Pascal; Bjamer, Ditlef; Dymek, Andrzej; Vermeulen, Jan H; Hultquist, Christer; Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma.; Chest; 2006; vol. 130 (no. 6); 1733-43

Study details

Secondary publication of another included study- see primary study for details	Secondary analysis, including paediatric participants only, of: O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/ formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005; 171:129 –136
Other publications associated with this study included in review	O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/ formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005; 171:129 –136. Included in review 3.2b
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Multinational
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by AstraZeneca
Inclusion criteria	Aged 4-11 years Asthma diagnosis for at least 6 months

	At least one clinically important exacerbation within 12 months Receiving ICS at a constant dose between 200-500 mcg per day for at least 3 months FEV1 60-100% of predicted and ≥12% reversibility after receiving SABA ≥8 SABA inhalations in the last 10 days of the run-in period
Exclusion criteria	>7 SABA inhalations on any single day of the run-in period Exacerbation or change in ICS medication during the run-in period
Recruitment / selection of participants	Recruited from 41 centres in 12 countries, method not reported
Intervention(s)	Following a run-in period where participants received their usual ICS therapy plus terbutaline as-needed for symptom relief, participants were allocated to one of three interventions: • 80/4.5 mcg budesonide/formoterol, one inhalation once per day plus additional inhalations as-needed for symptom relief (SMART) • 80/4.5 mcg budesonide/formoterol, one inhalation once per day plus 0.4 mg terbutaline as-needed for symptom relief (ICS/LABA + SABA) • 320 mcg budesonide, one inhalation once per day plus 0.4 mg terbutaline as-needed for symptom relief (ICS + SABA) All medications were administered via blinded Turbuhaler. Reliever medication could be used up to 7 times per day as-needed.
Population subgroups	**Exacerbations**

	Yes - exacerbation within 12 months was an inclusion criteria **Atopy** Not reported
Comparator	See interventions
Number of participants	341 randomised 118 received SMART, 109 completed 117 received ICS/LABA+SABA, 107 completed 106 received ICS+SABA, 92 completed
Duration of follow-up	12 months
Indirectness	None
Additional comments	ITT

Study arms

Regular paediatric moderate dose ICS plus SABA prn (N = 106)
320 mcg budesonide once daily plus 0.4 mg terbutaline as-needed for symptom relief

Regular paediatric low dose ICS/LABA plus SABA prn (N = 117)
80/4.5 mcg budesonide/formoterol once daily plus 0.4 mg terbutaline as-needed for symptom relief

Paediatric low dose ICS/formoterol MART (N = 118)
80/4.5 mcg budesonide/formoterol once daily plus additional inhalations as-needed for symptom relief

Characteristics

Arm-level characteristics

Characteristic	Regular paediatric moderate dose ICS plus SABA prn (N = 106)	Regular paediatric low dose ICS/LABA plus SABA prn (N = 117)	Paediatric low dose ICS/formoterol MART (N = 118)
% Female Sample size	n = 36 ; % = 34	n = 35 ; % = 30	n = 33 ; % = 28
Mean age (SD) Nominal	8	8	8
Mean age (SD) Range	4 to 11	4 to 11	4 to 11
Ethnicity White Sample size	n = 90 ; % = 85	n = 101 ; % = 86	n = 100 ; % = 85
Comorbidities Nominal	NR	NR	NR
Asthma control (Puffs per day) SABA use Nominal	1.6	1.6	1.7

Characteristic	Regular paediatric moderate dose ICS plus SABA prn (N = 106)	Regular paediatric low dose ICS/LABA plus SABA prn (N = 117)	Paediatric low dose ICS/formoterol MART (N = 118)
Asthma control (Puffs per day) SABA use Range	0.1 to 4	0.3 to 5.6	0.7 to 5.9
Lung function (% of predicted) FEV1 Nominal	76	76	76
Lung function (% of predicted) FEV1 Range	60 to 100	54 to 99	57 to 108
ICS dose Nominal	321	302	319
ICS dose Range	100 to 500	200 to 500	200 to 500

Outcomes

Study timepoints

- Baseline
- 12 month

Dichotomous Outcomes

Outcome	Regular paediatric moderate dose ICS plus SABA prn, Baseline, N = 106	Regular paediatric moderate dose ICS plus SABA prn, 12 month, N = 106	Regular paediatric low dose ICS/LABA plus SABA prn, Baseline, N = 117	Regular paediatric low dose ICS/LABA plus SABA prn, 12 month, N = 117	Paediatric low dose ICS/formoterol MART, Baseline, N = 118	Paediatric low dose ICS/formoterol MART, 12 month, N = 118
Severe asthma exacerbations Final values (defiined as requiring medical intervention (hospitalization/ED treatment, treatment with oral steroids, an increase in ICS [via a separate inhaler], and/or other additional treatment) No of events	n = NA ; % = NA	n = 21 ; % = 20	n = NA ; % = NA	n = 36 ; % = 31	n = NA ; % = NA	n = 10 ; % = 8
Adrenal insufficiency (morning cortisol <400 nmol/L) Final values, ICS n=41, ICS/LABA n=55, SMART n=51 No of events	n = NA ; % = NA	n = 3 ; % = 7	n = NA ; % = NA	n = 1 ; % = 2	n = NA ; % = NA	n = 2 ; % = 4
Pneumonia Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 2 ; % = 2	n = NA ; % = NA	n = 0 ; % = 0
Adverse events Final values No of events	n = NA ; % = NA	n = 5 ; % = 5	n = NA ; % = NA	n = 16 ; % = 13	n = NA ; % = NA	n = 2 ; % = 2

Severe asthma exacerbations - Polarity - Lower values are better
Adrenal insufficiency (morning cortisol <400 nmol/L) - Polarity - Lower values are better
Pneumonia - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Contrast Outcomes

Outcome	Paediatric low dose ICS/formoterol MART vs Regular paediatric moderate dose ICS plus SABA prn, Baseline, N2 = 106, N1 = 118	Paediatric low dose ICS/formoterol MART vs Regular paediatric moderate dose ICS plus SABA prn, 12 month, N2 = 106, N1 = 118	Paediatric low dose ICS/formoterol MART vs Regular paediatric low dose ICS/LABA plus SABA prn, Baseline, N2 = 117, N1 = 118	Paediatric low dose ICS/formoterol MART vs Regular paediatric low dose ICS/LABA plus SABA prn, 12 month, N2 = 117, N1 = 118	Regular paediatric low dose ICS/LABA plus SABA prn vs Regular paediatric moderate dose ICS plus SABA prn, Baseline, N2 = 106, N1 = 117	Regular paediatric low dose ICS/LABA plus SABA prn vs Regular paediatric moderate dose ICS plus SABA prn, 12 month, N2 = 106, N1 = 117
Reliever/rescue medication use (Puffs per day) Final values Mean (p value)	NA (NA)	-0.16 (0.1)	NA (NA)	-0.18 (0.038)	NA (NA)	0.02 (0.72)
Reliever/rescue medication use (reliever-free days) (% of days) Final values Mean (p value)	NA (NA)	5.4 (0.12)	NA (NA)	1.9 (0.48)	NA (NA)	3.5 (0.39)
Lung function (PEF) (Litres per	NA (NA)	17 (0.0019)	NA (NA)	13 (0.22)	NA (NA)	4 (0.053)

Outcome	Paediatric low dose ICS/formoterol MART vs Regular paediatric moderate dose ICS plus SABA prn, Baseline, N2 = 106, N1 = 118	Paediatric low dose ICS/formoterol MART vs Regular paediatric moderate dose ICS plus SABA prn, 12 month, N2 = 106, N1 = 118	Paediatric low dose ICS/formoterol MART vs Regular paediatric low dose ICS/LABA plus SABA prn, Baseline, N2 = 117, N1 = 118	Paediatric low dose ICS/formoterol MART vs Regular paediatric low dose ICS/LABA plus SABA prn, 12 month, N2 = 117, N1 = 118	Regular paediatric low dose ICS/LABA plus SABA prn vs Regular paediatric moderate dose ICS plus SABA prn, Baseline, N2 = 106, N1 = 117	Regular paediatric low dose ICS/LABA plus SABA prn vs Regular paediatric moderate dose ICS plus SABA prn, 12 month, N2 = 106, N1 = 117
minute) Final values Mean (p value)						

Reliever/rescue medication use - Polarity - Lower values are better
Reliever/rescue medication use (reliever-free days) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Continuous Outcomes

Outcome	Regular paediatric moderate dose ICS plus SABA prn, Baseline, N = 106	Regular paediatric moderate dose ICS plus SABA prn, 12 month, N = 106	Regular paediatric low dose ICS/LABA plus SABA prn, Baseline, N = 117	Regular paediatric low dose ICS/LABA plus SABA prn, 12 month, N = 117	Paediatric low dose ICS/formoterol MART, Baseline, N = 118	Paediatric low dose ICS/formoterol MART, 12 month, N = 118
Severe exacerbation rate Total number of events Nominal	NA	32	NA	52	NA	11

Severe exacerbation rate - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular low-moderate dose ICS plus SABA prn-Regular low dose ICS/LABA plus SABA prn-Regular low dose ICS/formoterol with ICS/formoterol prn -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adrenalinsufficiency(morningcortisol<400nmol/L)-NoOfEvents-Regular low-moderate dose ICS plus SABA prn-Regular low dose ICS/LABA plus SABA prn-Regular low dose ICS/formoterol with ICS/formoterol prn -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia-NoOfEvents-Regular low-moderate dose ICS plus SABA prn-Regular low dose ICS/LABA plus SABA prn-Regular low dose ICS/formoterol with ICS/formoterol prn -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular low-moderate dose ICS plus SABA prn-Regular low dose ICS/LABA plus SABA prn-Regular low dose ICS/formoterol with ICS/formoterol prn -t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Reliever/rescuemedicationuse-Regular paediatric moderate dose ICS plus SABA prn-Regular paediatric low dose ICS/LABA plus SABA prn-Paediatric low dose ICS/formoterol MART-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Reliever/rescuemedicationuse(reliever-freedays)-Regular paediatric moderate dose ICS plus SABA prn-Regular paediatric low dose ICS/LABA plus SABA prn-Paediatric low dose ICS/formoterol MART-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

ContrastOutcomes-Lungfunction(PEF)-Regular paediatric moderate dose ICS plus SABA prn-Regular paediatric low dose ICS/LABA plus SABA prn-Paediatric low dose ICS/formoterol MART-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Severeexacerbationrate-Nominal-Regular paediatric moderate dose ICS plus SABA prn-Regular paediatric low dose ICS/LABA plus SABA prn-Paediatric low dose ICS/formoterol MART-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

de Blic, 2009

Bibliographic Reference	de Blic, Jacques; Ogorodova, Ludmila; Klink, Rabih; Sidorenko, Irina; Valiulis, Arunas; Hofman, Jerzy; Bennedbaek, Olav; Anderton, Sally; Attali, Valerie; Desfougeres, Jean-Luc; Poterre, Marc; Salmeterol/fluticasone propionate vs. double dose fluticasone propionate on lung function and asthma control in children.; Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology; 2009; vol. 20 (no. 8); 763-71

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	International (Europe)
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by GlaxoSmithKline
Inclusion criteria	Children aged 4-11 years Asthma for ≥6 months

	FEV1 or PEF reversibility ≥15% Receiving 400 mcg per day beclomethasone dipropionate equiv. Asthma not controlled for ≥2 out of 4 weeks of the run-in on 100 mcg fluticasone dipropionate
Exclusion criteria	Respiratory tract infection, exacerbation or ER treatment within 4 weeks Hospitalisation due to asthma, or use of systemic corticosteroids in the past 3 months
Recruitment / selection of participants	Recruited from 46 sites in 12 countries, method not reported
Intervention(s)	Following a run-in period of 4 weeks where participants received 100 mcg fluticasone dipropionate twice daily, participants randomised to the intervention arm received 50/100 mcg salmeterol/fluticasone twice daily
Population subgroups	<u>Exacerbations</u> Hospitalisation due to asthma, or use of systemic corticosteroids in the past 3 months, were exclusion criteria. <u>Atopy</u> 84% atopic in ICS/LABA group, 91% atopic in ICS group
Comparator	Following a run-in period of 4 weeks where participants received 100 mcg fluticasone dipropionate twice daily, participants randomised to the comparison arm received 200 mcg fluticasone twice daily
Number of participants	321 randomised, 18 participants excluded from analysis due to compromised blinding at one study site 150 received ICS/LABA 153 received ICS monotherapy

Duration of follow-up	12 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular paediatric moderate dose ICS/LABA plus SABA prn (N = 150)
50/100 mcg salmeterol/fluticasone, one inhalation twice daily

Regular paediatric high dose ICS with SABA prn (N = 153)
100 mcg fluticasone, two inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular paediatric moderate dose ICS/LABA plus SABA prn (N = 150)	Regular paediatric high dose ICS with SABA prn (N = 153)
% Female Sample size	n = 53 ; % = 35	n = 55 ; % = 36
Mean age (SD) Nominal	8.1	8
Mean age (SD) Range	4 to 11	4 to 11
Ethnicity	NR	NR

Characteristic	Regular paediatric moderate dose ICS/LABA plus SABA prn (N = 150)	Regular paediatric high dose ICS with SABA prn (N = 153)
Nominal		
Comorbidities Nominal	NR	NR
ICS dose Nominal	NR	NR
Asthma control (Puffs per day) Daily SABA use Mean (SD)	0.4 (0.7)	0.5 (0.7)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Regular paediatric moderate dose ICS/LABA plus SABA prn, Baseline, N = 150	Regular paediatric moderate dose ICS/LABA plus SABA prn, 12 week, N = 150	Regular paediatric high dose ICS with SABA prn, Baseline, N = 153	Regular paediatric high dose ICS with SABA prn, 12 week, N = 153
Lung function (PEF) (Litres per	NA (NA)	26.9 (26.1)	NA (NA)	19.3 (26.2)

Outcome	Regular paediatric moderate dose ICS/LABA plus SABA prn, Baseline, N = 150	Regular paediatric moderate dose ICS/LABA plus SABA prn, 12 week, N = 150	Regular paediatric high dose ICS with SABA prn, Baseline, N = 153	Regular paediatric high dose ICS with SABA prn, 12 week, N = 153
minute) Change scores Mean (SD)				

Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular paediatric moderate dose ICS/LABA plus SABA prn, Baseline, N = 150	Regular paediatric moderate dose ICS/LABA plus SABA prn, 12 week, N = 150	Regular paediatric high dose ICS with SABA prn, Baseline, N = 153	Regular paediatric high dose ICS with SABA prn, 12 week, N = 153
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 2 ; % = 1	n = NA ; % = NA	n = 2 ; % = 1
Adverse events No of events	n = NR ; % = NR	n = 87 ; % = 58	n = NR ; % = NR	n = 86 ; % = 56

Severe asthma exacerbations - Polarity - Lower values are better

Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
ContinuousOutcomes-Lungfunction(PEF)-MeanSD-Regular low dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information on pre-specified analyses in a protocol)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular low dose ICS/LABA-Regular moderate-high dose ICS-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information on pre-specified analyses in a protocol)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents(n=150;153)-NoOfEvents-Regular low dose ICS/LABA plus SABA prn-Regular low/moderate dose ICS with SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information on pre-specified analyses in a protocol)*
Overall bias and Directness	Overall Directness	Directly applicable

Lenney, 2013

Bibliographic Reference	Lenney, W; McKay, AJ; Tudur Smith, C; Williamson, PR; James, M; Price, D; Management of Asthma in School age Children On Therapy (MASCOT): a randomised, double-blind, placebo-controlled, parallel study of efficacy and safety; Health technology assessment (Winchester, England); 2013; vol. 17 (no. 4); 1-218

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	ISRCTN03556343.
Study type	Randomised controlled trial (RCT)
Study location	England and Scotland
Study setting	Primary and secondary care sites in England and Scotland
Study dates	Randomisation from may 2009. Trial being closed prematurely on 24 June 2010
Sources of funding	NIHR HTA programme
Inclusion criteria	1. Children with asthma aged from 6 years to 14 years 11 months. 2. Children who required frequent short-acting beta-2 agonist relief therapy: seven or more puffs in the past 7 days.

	3. Children with symptoms of asthma (i.e. wheeze, shortness of breath but not cough alone) resulting in: i. nocturnal wakening in the last week and/or ii. interference with usual activities in the last week. 4. Continuing consent/assent (where appropriate)
Exclusion criteria	1. Children whose asthma was controlled after the 4 week run-in, in which control was defined as the absence of any symptoms of asthma (except cough alone) or when the symptoms of asthma had not interfered with usual activities in the last week. 2. Children who were receiving long-acting beta-2 agonists, leukotriene receptor antagonists, regular theophylline therapy or high-dose ICSs (>1000µg) and unlicensed beclometasone dipropionate or equivalent (at the discretion of the investigator). 3. Children with other respiratory diseases, cystic fibrosis, cardiac disease or immunological disorders
Recruitment / selection of participants	The main strategies for identifying eligible patients were from secondary care referrals (outpatients and inpatients) and from general practice database searches. The searches were followed by one mail-out inviting participation in the study. As recruitment proved difficult, further strategies were developed during the study.
Intervention(s)	Inhaled fluticasone propionate 100µg and salmeterol 50µg twice daily (combination inhaler) plus placebo tablet once daily (n=23) Inhaled fluticasone propionate 100µg twice daily plus montelukast 5-mg tablet once daily (n=21)
Population subgroups	Exacerbations: patients who have had exacerbations entered (defined as a short course of oral corticosteroids, and unscheduled GP or A&E Department visit or a hospital admission within the previous 6 months) were included. Atopy: No additional information.
Comparator	Inhaled fluticasone propionate 100µg twice daily plus placebo tablet once daily (n=19)
Number of participants	63
Duration of follow-up	24 weeks and 48 weeks
Indirectness	Indirectness for population (age range up to 14 years).

Additional comments	All primary analyses are based on an intention-to-treat (ITT) principle as far as practically possible. All count data (number of exacerbations, number of school days missed and number of hospital admissions) were analysed using Poisson regression with adjustment of standard errors [multiplying by the square root of the scale parameter estimated as the Pearson's chi-squared statistic divided by its degrees of freedom (df)] to account for overdispersion. Adjustment for centre in the regression model was originally planned in the protocol but, as recognised in the SAP (see Appendix 2), was felt to be impracticable because of the limited number of patients randomised.

Study arms

Regular paediatric moderate dose ICS with SABA prn (N = 19)
Inhaled fluticasone propionate 100µg twice daily plus placebo tablet once daily

Regular paediatric moderate dose ICS/LABA plus SABA prn (N = 23)
Inhaled fluticasone propionate 100µg and salmeterol 50µg twice daily (combination inhaler) plus placebo tablet once daily

Regular paediatric moderate dose ICS with montelukast plus SABA prn (N = 21)
Inhaled fluticasone propionate 100µg twice daily plus montelukast 5-mg tablet once daily

Characteristics

Arm-level characteristics

Characteristic	Regular paediatric moderate dose ICS with SABA prn (N = 19)	Regular paediatric moderate dose ICS/LABA plus SABA prn (N = 23)	Regular paediatric moderate dose ICS with montelukast plus SABA prn (N = 21)
% Female Sample size	n = 2 ; % = 10.5	n = 10 ; % = 43.5	n = 11 ; % = 52.4

Characteristic	Regular paediatric moderate dose ICS with SABA prn (N = 19)	Regular paediatric moderate dose ICS/LABA plus SABA prn (N = 23)	Regular paediatric moderate dose ICS with montelukast plus SABA prn (N = 21)
Mean age (SD) Mean (SD)	10.37 (1.82)	10.46 (2.33)	10.33 (2.37)
FEV1 % Mean (SD)	88.29 (17.55)	79.79 (19.9)	86.47 (13.32)

Outcomes

Study timepoints

- Baseline
- 48 week

Dichotomous outcomes

Outcome	Regular paediatric moderate dose ICS with SABA prn, Baseline, N = 19	Regular paediatric moderate dose ICS with SABA prn, 48 week, N = 11	Regular paediatric moderate dose ICS/LABA plus SABA prn, Baseline, N = 23	Regular paediatric moderate dose ICS/LABA plus SABA prn, 48 week, N = 15	Regular paediatric moderate dose ICS with montelukast plus SABA prn, Baseline, N = 21	Regular paediatric moderate dose ICS with montelukast plus SABA prn, 48 week, N = 12
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 1 ; % = 9.1	n = NA ; % = NA	n = 5 ; % = 33.3	n = NA ; % = NA	n = 1 ; % = 8.3
Adverse events Final values (ICS,	n = NA ; % = NA	n = 17 ; % = 89	n = NA ; % = NA	n = 18 ; % = 78	n = NA ; % = NA	n = 18 ; % = 86

Outcome	Regular paediatric moderate dose ICS with SABA prn, Baseline, N = 19	Regular paediatric moderate dose ICS with SABA prn, 48 week, N = 11	Regular paediatric moderate dose ICS/LABA plus SABA prn, Baseline, N = 23	Regular paediatric moderate dose ICS/LABA plus SABA prn, 48 week, N = 15	Regular paediatric moderate dose ICS with montelukast plus SABA prn, Baseline, N = 21	Regular paediatric moderate dose ICS with montelukast plus SABA prn, 48 week, N = 12
ICS/LABA, ICS+mont n's= 19, 23, 21) No of events						
Hospital admissions Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 2 ; % = 13.3	n = NA ; % = NA	n = 0 ; % = 0

Severe asthma exacerbations - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better

Continuous outcomes

Outcome	Regular paediatric moderate dose ICS with SABA prn, Baseline, N = 19	Regular paediatric moderate dose ICS with SABA prn, 48 week, N = 10	Regular paediatric moderate dose ICS/LABA plus SABA prn, Baseline, N = 23	Regular paediatric moderate dose ICS/LABA plus SABA prn, 48 week, N = 15	Regular paediatric moderate dose ICS with montelukast plus SABA prn, Baseline, N = 21	Regular paediatric moderate dose ICS with montelukast plus SABA prn, 48 week, N = 12
Quality of life (Paediatric Asthma Quality of Life Questionnaire)	NA (NA)	1.29 (0.61)	NA (NA)	1.1 (1.86)	NA (NA)	1.84 (1.66)

Outcome	Regular paediatric moderate dose ICS with SABA prn, Baseline, N = 19	Regular paediatric moderate dose ICS with SABA prn, 48 week, N = 10	Regular paediatric moderate dose ICS/LABA plus SABA prn, Baseline, N = 23	Regular paediatric moderate dose ICS/LABA plus SABA prn, 48 week, N = 15	Regular paediatric moderate dose ICS with montelukast plus SABA prn, Baseline, N = 21	Regular paediatric moderate dose ICS with montelukast plus SABA prn, 48 week, N = 12
Scale range: 1-7, change scores Mean (SD)						
Lung Function (FEV1) (% of predicted) Change scores (ICS, ICS/LABA, ICS+Mont n's= 8, 13, 9) Mean (SD)	NA (NA)	0.12 (12.74)	NA (NA)	15.54 (19.77)	NA (NA)	4.55 (15.83)

Quality of life (Paediatric Asthma Quality of Life Questionnaire) - Polarity - Higher values are better
Lung Function (FEV1) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Dichotomousoutcomes-Exacerbationsrequiringcourseoforalsteroids-NoOfEvents-Fluticasone propionate 100ug BID-Inhaled fluticasone propionate 100µg and salmeterol 50µg BID-Inhaled fluticasone propionate 100µg BID plus montelukast 5-mg tablet once daily-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Rates for missing data greater than event rate, though even across arms)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-PAQLQ-s(Pediatricasthmaqualityoflifequestionnairewithstandardisedactivities)-MeanSD-Fluticasone propionate 100ug BID-Inhaled fluticasone propionate 100µg and salmeterol 50µg BID-Inhaled fluticasone propionate 100µg BID plus montelukast 5-mg tablet once daily-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(High rates of missing data ((35-47%) and varies across arms)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Lungfunction(FEV1%predicted)[n=8;13;9)-MeanSD-Regular paediatric moderate dose ICS with SABA prn-Regular paediatric moderate dose ICS/LABA plus SABA prn-Regular paediatric moderate dose ICS with montelukast plus SABA prn-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(>10% missing data in one trial compared to others. 24 week analysis post-hoc sue to early closure of trial)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Hospitaladmissions-NoOfEvents-Regular paediatric moderate dose ICS with SABA prn-Regular paediatric moderate dose ICS/LABA plus SABA prn-Regular paediatric moderate dose ICS with montelukast plus SABA prn-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Missing data > rate of events and unbalanced across arms)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Adverseevents-NoOfEvents-Regular paediatric moderate dose ICS with SABA prn-Regular paediatric moderate dose ICS/LABA plus SABA prn-Regular paediatric moderate dose ICS with montelukast plus SABA prn-t48

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Rates for missing data greater than event rate, though even across arms)*
Overall bias and Directness	Overall Directness	Directly applicable

Malone, 2005

Bibliographic Reference	Malone, Randolph; LaForce, Craig; Nimmagadda, Sai; Schoaf, Lynne; House, Karen; Ellsworth, Anna; Dorinsky, Paul; The safety of twice-daily treatment with fluticasone propionate and salmeterol in pediatric patients with persistent asthma.; Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology; 2005; vol. 95 (no. 1); 66-71

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study conducted in 66 in the United States and 13 sites in Canada.
Study setting	Outpatients setting
Study dates	Study conducted between April 2002 to January 2003
Sources of funding	GlaxoSmithKline
Inclusion criteria	Boys and premenarchal girls aged 4 to 11 years with asthma, as defined by the American Thoracic Society criteria for at least 2 months and were receiving ICS at a consistent dose for at least 1 month before screening.

	Patients aged 6 to 11 years were required to have a FEV1 of 50% to 95% of the Polgar predicted value ; patients aged 4 to 5 years were required to have a morning PEFR of 50% to 95% of the Polgar predicted value. Patients were also required to demonstrate an increase in FEV1 (for patients aged 6 –11 years) or morning PEFR (for patients aged 4 –5 years) of 12% or more within 30 minutes of inhalation of 2 to 4 actuations of albuterol (180 –360 ug) or to have historical documentation of 12% or greater reversibility within the previous year. Further inclusion criteria identified through 2 week run-in period: a daytime asthma symptom score of at least 1 (on a scale from 0 to 5) on 3 or more days or the use of albuterol on 3 or more days during the 7 days before the randomization visit, and (3) adequate compliance, defined as 70% or greater compliance with diary card completion.
Exclusion criteria	History of life-threatening asthma; hospitalization due to asthma twice or more in the previous year; a significant concurrent disease (eg, cystic fibrosis, malignancy, or immunologic compromise); recent upper or lower respiratory tract infection; current chickenpox or recent exposure to chickenpox in a nonimmune patient; severe milk protein allergy; hypersensitivity to beta 2-agonist, sympathomimetic, or corticosteroid therapy; clinically significant abnormal laboratory test results; a history or present use of tobacco; and a history or current presence of glaucoma or posterior subcapsular cataracts. Patients were required not to have used oral or parenteral corticosteroids for at least 1 month before screening, cromolyn or nedocromil for at least 1 week before screening, or long-acting beta 2-agonists within 48 hours of screening and throughout the study. In addition, the use of medications that could affect the course of asthma or interact with study medications (eg, anticholinergics, anticonvulsants, or beta-adrenergic blockers) was prohibited throughout the study.
Recruitment / selection of participants	No additional information
Intervention(s)	Fluticasone propionate-salmeterol (100/50ug) BID N=101 Fluticasone propionate (100ug) and salmeterol (50ug) twice daily. One inhalation in the morning and one in the evening approx 12 hours apart.
Population subgroups	Exacerbations: History of life-threatening asthma; hospitalization due to asthma twice or more in the previous year were exclusion criteria. Patients were required not to have used oral or parenteral corticosteroids for at least 1 month before screening.

	Atopy: No additional information.
Comparator	Fluticasone propionate 100ug BID N=102 Fluticasone propionate (100ug) twice daily. One inhalation in the morning and one in the evening approx 12 hours apart.
Number of participants	203
Duration of follow-up	12 weeks
Additional comments	The intent-to-treat population, which included all patients who were randomized and received at least 1 dose of study drug, was the primary population used for all demographic and safety measures except for cortisol excretion. For patients who withdrew from the study prematurely, all available data up to the time of discontinuation were included in the intent-to-treat population. Cortisol outcomes: The cortisol population, the primary population for urinary cortisol analyses, was defined as the intent-to-treat population excluding patients with 1 or more of the following: urine volume less than 300 mL (for patients aged 4 –5 years) or less than 400 mL (for patients aged 6 –11 years) and 24-hour creatinine excretion below a predefined threshold range; a collection time that was not less than 24 +/- 4 hours in duration; oral, parenteral, or topical (>=1% hydrocortisone) corticosteroid use within 30 days of visit 1 or during the study; not taking the study drug for more than 1 day before the start of urine collection; and failure to have both a baseline and a posttreatment urine collection. Urinary cortisol excretion values were not corrected for creatinine.

Study arms

Regular paediatric moderate dose ICS/LABA with SABA prn (N = 101)
Fluticasone propionate (100ug) and salmeterol (50ug) twice daily. One inhalation in the morning and one in the evening approx 12 hours apart.

Regular paediatric moderate dose ICS with SABA prn (N = 102)
Fluticasone propionate (100ug) twice daily. One inhalation in the morning and one in the evening approx 12 hours apart.

Characteristics

Arm-level characteristics

Characteristic	Regular paediatric moderate dose ICS/LABA with SABA prn (N = 101)	Regular paediatric moderate dose ICS with SABA prn (N = 102)
% Female Sample size	n = 32 ; % = 31.7	n = 41 ; % = 40.2
Mean age (SD) Sample size	n = NR ; % = NR	n = NR ; % = NR
Mean age (SD) Mean (SD)	8 (NR)	8.1 (NR)
4-5 years Sample size	n = 21 ; % = 21	n = 19 ; % = 19
4-5 years Mean (SD)	NR (NR)	NR (NR)
6-11 years Sample size	n = 80 ; % = 79	n = 83 ; % = 81
6-11 years Mean (SD)	NR (NR)	NR (NR)
White Sample size	n = 68 ; % = 67	n = 74 ; % = 72

Characteristic	Regular paediatric moderate dose ICS/LABA with SABA prn (N = 101)	Regular paediatric moderate dose ICS with SABA prn (N = 102)
Black Sample size	n = 23 ; % = 23	n = 16 ; % = 16
Other Sample size	n = 10 ; % = 10	n = 12 ; % = 12
Duration of asthma (years) Mean (SD)	5.3 (NR)	5.1 (NR)
FEV1% predicted in patients aged 6-11 years Mean (SD)	80.9 (NR)	80 (NR)
PEFR (L/min) in patients aged 4-5 years Mean (SD)	140 (NR)	145 (NR)
Fluticasone propionate Sample size	n = 75 ; % = 74	n = 71 ; % = 70
Fluticasone propionate Mean (SD)	166 (NR)	167 (NR)
Budesnonide Sample size	n = 24 ; % = 24	n = 27 ; % = 26

Characteristic	Regular paediatric moderate dose ICS/LABA with SABA prn (N = 101)	Regular paediatric moderate dose ICS with SABA prn (N = 102)
Budesnonide Mean (SD)	400 (NR)	360 (NR)
Beclomethasone dipropionate HFA Sample size	n = 1 ; % = 1	n = 1 ; % = 1
Beclomethasone dipropionate HFA Mean (SD)	160 (NR)	320 (NR)
Beclomethasone dipropionate CFC Sample size	n = 0 ; % = 0	n = 1 ; % = 1
Beclomethasone dipropionate CFC Mean (SD)	NA (NA)	252 (NR)
Triamcinolone acetonide Sample size	n = 1 ; % = 1	n = 2 ; % = 2
Triamcinolone acetonide Mean (SD)	600 (NR)	500 (NR)

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous outcomes

Outcome	Regular paediatric moderate dose ICS/LABA with SABA prn, Baseline, N = 101	Regular paediatric moderate dose ICS/LABA with SABA prn, 12 week, N = 101	Regular paediatric moderate dose ICS with SABA prn, Baseline, N = 102	Regular paediatric moderate dose ICS with SABA prn, 12 week, N = 102
Adverse events Final values No of events	n = NA ; % = NA	n = 60 ; % = 59	n = NA ; % = NA	n = 58 ; % = 57
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 3 ; % = 3	n = NA ; % = NA	n = 8 ; % = 8
Pneumonia (lower respiratory tract infections) Final values No of events	n = NA ; % = NA	n = 1 ; % = 1	n = NA ; % = NA	n = 3 ; % = 3

Adverse events - Polarity - Lower values are better
Severe asthma exacerbations - Polarity - Lower values are better
Pneumonia (lower respiratory tract infections) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Dichotomousoutcomes-Adverseevent(%ofpatients)-NoOfEvents-Fluticasone propionate-salmeterol (100/50ug) BID-Fluticasone propionate 100ug BID-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about randomisation process or protocol)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Asthmaexacerbations-NoOfEvents-Fluticasone propionate-salmeterol (100/50ug) BID-Fluticasone propionate 100ug BID-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about randomisation process or protocol)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Pneumonia(lowerrespiratorytractinfections)-NoOfEvents-Regular paediatric moderate dose ICS/LABA with SABA prn-Regular paediatric moderate dose ICS with SABA prn-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about randomisation process or protocol)*
Overall bias and Directness	Overall Directness	Directly applicable

Morice, 2008

Bibliographic Reference	Morice, Alyn H; Peterson, Stefan; Beckman, Ola; Kukova, Zuzana; Efficacy and safety of a new pressurised metered-dose inhaler formulation of budesonide/formoterol in children with asthma: a superiority and therapeutic equivalence study.; Pulmonary pharmacology & therapeutics; 2008; vol. 21 (no. 1); 152-9

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	SD-039-0682
Study location	Multicentre study conducted in 53 sites across 8 countries (Argentina, Brazil, Denmark, Hong Kong, Mexico, Polan, Slovakia and Taiwan)
Study setting	Paediatric outpatients
Study dates	No additional information
Sources of funding	Astrazeneca
Inclusion criteria	Children aged 6–11 years) with asthma for >=6 months and PEF >=50% of predicted normal (pre-bronchodilator) were recruited. To be eligible for inclusion, all patients had to have a history of daily ICS use (stable dose of 375 to 1000 mg/day within the 30 days prior to enrolment) and clinically important exercise-induced bronchoconstriction (>=1 episode/week) for

	>=3 months before enrolment. Patients also had to demonstrate the ability to use a DPI, pMDI and peak flow meter correctly. Run-in period: a 10-14 days, during which they continued their pre-study ICS medication (stable dose of 37 5to 1000 mg=day), Before randomisation, all patients had to have a total asthma symptom score >=1 on >=4 of the last 7 days of run-in (scale: 0 = no symptoms; 1 = aware of symptoms but can tolerate them easily; 2 = asthma causing enough discomfort to interfere with normal activities or sleep; 3 = unable to perform normal activities or sleep because of asthma day- and night-time scores were summed) and a mean morning PEF 50–85% of their post-bronchodilatory PEF (measured at enrolment 15 min after inhalation of terbutaline 1 mg) during the last 7 days of run-in.
Exclusion criteria	No additional information
Recruitment / selection of participants	No additional information
Intervention(s)	Budesonide/formoterol (80/4.5ug) DPI and pMDI two inhalations twice daily Combination of two arms in the trial: Budesonide/formoterol DPI 80/4.5 ug Budesonide/formoterol pMDI 80/4.5 ug

	Concomitant therapy: All patients were given the inhaled short-acting b2-agonist, terbutaline 0.5 mg/inhalation, for symptom relief. If the subject preferred another short-acting b2-agonist that was regarded as being equivalent in clinical practice, e.g. salbutamol, it was prescribed by the investigator. It was, however, important that the subject used the same brand and strength of rescue medication throughout the study.
Population subgroups	Exacerbations: clinically important exercise-induced bronchoconstriction (>=1 episode/week) for >=3 months before enrolment was an inclusion criteria Atopy: no additional information.
Comparator	Budesonide pMDI 100 mg (pMDI) two inhalations twice daily Concomitant therapy: All patients were given the inhaled short-acting b2-agonist, terbutaline 0.5 mg/inhalation, for symptom relief. If the subject preferred another short-acting b2-agonist that was regarded as being equivalent in clinical practice, e.g. salbutamol, it was prescribed by the investigator. It was, however, important that the subject used the same brand and strength of rescue medication throughout the study.
Number of participants	622
Duration of follow-up	12 weeks
Additional comments	Intention-to-treat

Study arms

Regular paediatric moderate dose ICS/LABA plus SABA prn (N = 415)

Budesonide/formoterol DPI 80/4.5 ug two inhalations twice daily or Budesonide/formoterol pMDI 80/4.5 ug two inhalations twice daily
two study arms combined for this review

Regular paediatric moderate dose ICS with SABA prn (N = 207)
Budesonide pMDI 100ug two inhalations twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular paediatric moderate dose ICS/LABA plus SABA prn (N = 415)	Regular paediatric moderate dose ICS with SABA prn (N = 207)
% Female Sample size	n = 142 ; % = 34.2	n = 70 ; % = 33.8
Mean age (SD) Mean (SD)	8 (NR)	9 (NR)
Median time since diagnosis Median (IQR)	3 (NR to NR)	3 (NR to NR)
PEF % predicted Mean (SD)	82.5 (NR)	82 (NR)
FEV1 % predicted Mean (SD)	89 (NR)	87 (NR)
ICS at entry Mean (SD)	464 (NR)	475 (NR)
Reliever medication use (inhalations/day)	0.9 (NR)	1.1 (NR)

Characteristic	Regular paediatric moderate dose ICS/LABA plus SABA prn (N = 415)	Regular paediatric moderate dose ICS with SABA prn (N = 207)
Mean (SD)		
Total asthma symptom score 0-6 scale Mean (SD)	1.55 (NR)	1.7 (NR)
Symptom-free days (%) Mean (SD)	18.5 (NR)	16 (NR)
PAQLQ (S) overall score range 1-7 Mean (SD)	5.55 (NR)	5.43 (NR)

Outcomes

Study timepoints

- Baseline
- 12 week

Dichotomous outcones

Outcome	Regular paediatric moderate dose ICS/LABA plus SABA prn, Baseline, N = 415	Regular paediatric moderate dose ICS/LABA plus SABA prn, 12 week, N = 415	Regular paediatric moderate dose ICS with SABA prn , Baseline, N = 207	Regular paediatric moderate dose ICS with SABA prn , 12 week, N = 207
Adverse events	n = NA ; % = NA	n = 192 ; % = 46	n = NA ; % = NA	n = 81 ; % = 39

Outcome	Regular paediatric moderate dose ICS/LABA plus SABA prn, Baseline, N = 415	Regular paediatric moderate dose ICS/LABA plus SABA prn, 12 week, N = 415	Regular paediatric moderate dose ICS with SABA prn , Baseline, N = 207	Regular paediatric moderate dose ICS with SABA prn , 12 week, N = 207
Final values No of events				

Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Dichotomousoutcones-Adverseevents-NoOfEvents-Budesonide/formoterol (80/4.5ug) DPI and pMDI-Budesonide pMDI 100ug-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about pre-specified analyses in a protocol)*
Overall bias and Directness	Overall Directness	Directly applicable

Pearlman, 2017

Bibliographic Reference	Pearlman, David S; Eckerwall, Goran; McLaren, Julie; Lamarca, Rosa; Puu, Margareta; Gilbert, Ileen; Jorup, Carin; Sandin, Kristina; Lanz, Miguel J; Efficacy and safety of budesonide/formoterol pMDI vs budesonide pMDI in asthmatic children (6-<12 years).; Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology; 2017; vol. 118 (no. 4); 489-499e1

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT02091986 (Clinical trials gov)
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study (88 sites in United States, Mexico, Panama and Slovakia)
Study setting	No additional information.
Study dates	Participant enrollment was from April 2014 to April 2016
Sources of funding	Astrazeneca LP
Inclusion criteria	Age 6 to <12 years with a documented clinical diagnosis of asthma as defined by the American Thoracic Society for at least 6 months before the run-in visit (visit 2). Patients were required to have used moderate-dose ICS or, alternatively, fixed-

	dose ICS plus LABA for at least 4 weeks before enrollment (visit 1). Patients on fixed-dose ICS plus LABA were switched to a comparable dose of ICS without LABA for at least 48 hours before the run-in visit. Before randomization (visit 3), FEV1 reversibility of at least 12% from pre-bronchodilator levels within 15 to 30 minutes after administration of a standard and equivalent dose of 2 to 4 inhalations of albuterol (90 mg per inhalation, labeled to reflect the dose delivered by the actuator mouthpiece; in the United States) or salbutamol (100 mg per inhalation, labeled to reflect the dose delivered from the canister valve; outside the United States) with or without a spacer or either drug given by nebulizer (2.5 mg) was required. At the run-in visit, patients were required to have a morning pre-bronchodilator clinic FEV1 value of 60% to 100% of predicted normal (measured 6 hours after the last dose of a short-acting b2-agonist [SABA] and 48 hours after the last dose of a LABA). Eligible patients demonstrated the ability to use a DPI for the run-in period and pMDI for the post-randomization period. To be eligible for randomisation patients were required during the run-in to have a total combined nighttime and daytime asthma symptom score of at least 1 (0 no symptoms; 1 mild symptoms; 2 moderate symptoms; 3 severe symptoms) or use of rescue medication on at least 4 of 7 consecutive days immediately prior to randomisation.
Exclusion criteria	Hospitalization or emergency treatment for asthma within 6 months before enrollment, treatment, for any reason, with systemic corticosteroids within 6 weeks before enrollment or during the run-in period, or with a b-blocker (including eye drops), or omalizumab, or other monoclonal or polyclonal antibody therapy within 6 months before the run-in visit. Patients with a significant disease (other than asthma) were excluded if, in the opinion of the investigator, the condition would place them at risk during study participation, could affect their ability to participate in the study, or could influence results from the study.
Recruitment / selection of participants	No additional information.
Intervention(s)	Budesonide (160ug) /Formoterol (9 or 4.5ug) pMDI (n=187)

	Combination of 2 arms in the trial: budesonide/formoterol pMDI 80/4.5ug x 2 inhalations (160/9ug) BID (n=92); budesonide/formoterol pMDI 80/2.25ug x 2 inhalations (160/4.5ug) BID (n=95). Concomitant therapy: patients could use study-provided albuterol or salbutamol as needed. Prophylactic use of SABA for exercise-induced bronchoconstriction was permitted up to 2 times per week, if part of a regular exercise regimen.
Population subgroups	Exacerbations: Hospitalization or emergency treatment for asthma within 6 months before enrollment was an exclusion criteria. Atopy: no additional information.
Comparator	Budesonide (160ug) pMDI (n=92) Budesonide pMDI, 80ug x 2 inhalations (160ug) BID Concomitant therapy: patients could use study-provided albuterol or salbutamol as needed. Prophylactic use of SABA for exercise-induced bronchoconstriction was permitted up to 2 times per week, if part of a regular exercise regimen.
Number of participants	279

Duration of follow-up	12 weeks
Indirectness	
Additional comments	The efficacy analysis set included all randomized patients who received at least 1 dose of study medication and contributed post-baseline data for at least 1 efficacy end point. The safety analysis set included all randomized patients who took at least 1 dose of study medication and for whom data were collected after randomization. Primary analysis was based on all available data, regardless of whether patients had discontinued study treatment.

Study arms

Regular paediatric moderate dose ICS/LABA with SABA prn (N = 187)

Budesonide/formoterol pMDI 80/4.5ug x 2 inhalations (160/9ug) BID (n=92); budesonide/formoterol pMDI 80/2.25ug x 2 inhalations (160/4.5ug) BID (n=95) *two study arms combined for this review*

Regular paediatric moderate dose ICS with SABA prn (N = 92)

Budesonide pMDI, 80ug x 2 inhalations (160ug) BID

Characteristics

Arm-level characteristics

Characteristic	Regular paediatric moderate dose ICS/LABA with SABA prn (N = 187)	Regular paediatric moderate dose ICS with SABA prn (N = 92)
% Female Sample size	n = 76 ; % = 40.6	n = 37 ; % = 40.2
Mean age (SD) Sample size	n = NR ; % = NR	n = NR ; % = NR
Mean age (SD)	9 (1.6)	9 (1.4)

Characteristic	Regular paediatric moderate dose ICS/LABA with SABA prn (N = 187)	Regular paediatric moderate dose ICS with SABA prn (N = 92)
Mean (SD)		
6-<9 years Sample size	n = 66 ; % = 35.3	n = 32 ; % = 34.8
6-<9 years Mean (SD)	NR (NR)	NR (NR)
9-<12 years Sample size	n = 121 ; % = 64.7	n = 60 ; % = 65.2
9-<12 years Mean (SD)	NR (NR)	NR (NR)
White Sample size	n = 121 ; % = 64.7	n = 53 ; % = 57.6
Black or African American Sample size	n = 50 ; % = 26.7	n = 26 ; % = 28.3
Asian Sample size	n = 0 ; % = 0	n = 2 ; % = 2.2
Native Hawaiian or other Pacific Islander Sample size	n = 1 ; % = 0.5	n = 0 ; % = 0
American Indian or Alaskan Native	n = 5 ; % = 2.7	n = 3 ; % = 3.3

Characteristic	Regular paediatric moderate dose ICS/LABA with SABA prn (N = 187)	Regular paediatric moderate dose ICS with SABA prn (N = 92)
Sample size		
Other Sample size	n = 8 ; % = 4.3	n = 7 ; % = 7.6
Unknown Sample size	n = 2 ; % = 1.1	n = 1 ; % = 1.1
Hispanic or Latino Sample size	n = 74 ; % = 39.6	n = 32 ; % = 34.8
Non-hispanic or Latino Sample size	n = 113 ; % = 60.4	n = 60 ; % = 65.2
Asthma duration (years) Mean (SD)	5.85 (3.1)	6.2 (3.2)
Low Sample size	n = 9 ; % = 4.8	n = 4 ; % = 4.3
Moderate Sample size	n = 170 ; % = 90.9	n = 82 ; % = 89.1
High Sample size	n = 6 ; % = 3.2	n = 1 ; % = 1.1
Not classified	n = 2 ; % = 1.1	n = 5 ; % = 5.4

Characteristic	Regular paediatric moderate dose ICS/LABA with SABA prn (N = 187)	Regular paediatric moderate dose ICS with SABA prn (N = 92)
Sample size		
Patients receiving ICA/LABA Previous medication Sample size	n = 52 ; % = 27.8	n = 19 ; % = 21.1
Symptom score (0-no sumptoms; 1-mild symptoms; 2-moderate symptoms; 3-severe symptoms) Mean (SD)	1.05 (0.6)	1 (0.58)
% of nighttime awakenings due to asthma symptoms From 6 days up to and including morning record at randomisation Mean (SD)	20 (27.62)	16.5 (25.16)
Total daily reliever medication use (inhalations/day) Mean (SD)	1.5 (2.04)	1.2 (1.52)
FEV1 (L) n=175; n=88 Mean (SD)	1.57 (0.38)	1.62 (0.36)
FEV1 % predicted n=175; n=88 Mean (SD)	75 (12.2)	73.8 (10.3)

Characteristic	Regular paediatric moderate dose ICS/LABA with SABA prn (N = 187)	Regular paediatric moderate dose ICS with SABA prn (N = 92)
PAQLQ score Mean (SD)	5.49 (1.08)	5.53 (1.14)

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous outcomes

Outcome	Regular paediatric moderate dose ICS/LABA with SABA prn, Baseline, N = 183	Regular paediatric moderate dose ICS/LABA with SABA prn, 12 week, N = 183	Regular paediatric moderate dose ICS with SABA prn, Baseline, N = 90	Regular paediatric moderate dose ICS with SABA prn, 12 week, N = 90
Reliever/rescue medication use (inhalations/day) Change score, seven-day average Mean (SD)	NA (NA)	-0.9 (2.1)	NA (NA)	-0.7 (1.37)
Lung function (PEF) (L/min) Change score, average across study period (ICS/LABA and ICS n's=149 and 72) Mean (SD)	NA (NA)	22 (54.2)	NA (NA)	19 (51.6)

Reliever/rescue medication use - Polarity - Lower values are better

Lung function (PEF) - Polarity - Higher values are better

Dichotomous outcomes

Outcome	Regular paediatric moderate dose ICS/LABA with SABA prn, Baseline, N = 183	Regular paediatric moderate dose ICS/LABA with SABA prn, 12 week, N = 183	Regular paediatric moderate dose ICS with SABA prn, Baseline, N = 90	Regular paediatric moderate dose ICS with SABA prn, 12 week, N = 90
Mortality No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 20 ; % = 10.9	n = NA ; % = NA	n = 12 ; % = 13.3
Adverse events Final values No of events	n = NA ; % = NA	n = 83 ; % = 45.3	n = NA ; % = NA	n = 40 ; % = 44.4

Mortality - Polarity - Lower values are better

Severe asthma exacerbations - Polarity - Lower values are better

Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Dichotomousoutcomes-Mortality-NoOfEvents-Budesonide (160ug) /Formoterol (9 or 4.5ug) pMDI -Budesonide (160ug) pMDI-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about adherence or how handled in analyses and no protocol to assess pre-specification of analyses)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-Totaldailyrelievermedicationuse-MeanSD-Budesonide (160ug) /Formoterol (9 or 4.5ug) pMDI -Budesonide (160ug) pMDI-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about adherence or how handled in analyses and no protocol to assess pre-specification of analyses)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuousoutcomes-MorningPEF(n=149;n=72-MeanSD-Budesonide (160ug) /Formoterol (9 or 4.5ug) pMDI -Budesonide (160ug) pMDI-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about adherence or how handled in analyses and no protocol to assess pre-specification of analyses)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Asthmaexacerbations-NoOfEvents-Budesonide (160ug) /Formoterol (9 or 4.5ug) pMDI -Budesonide (160ug) pMDI-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about adherence or how handled in analyses and no protocol to assess pre-specification of analyses)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Adverseevents-NoOfEvents-Budesonide (160ug) /Formoterol (9 or 4.5ug) pMDI -Budesonide (160ug) pMDI-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about adherence or how handled in analyses and no protocol to assess pre-specification of analyses)*
Overall bias and Directness	Overall Directness	Directly applicable

Vaessen-Verberne, 2010

Bibliographic Reference	Vaessen-Verberne, A.A.P.H.; Van Den Berg, N.J.; Van Nierop, J.C.; Brackel, H.J.L.; Gerrits, G.P.J.M.; Hop, W.C.J.; Duiverman, E.J.; Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma; American Journal of Respiratory and Critical Care Medicine; 2010; vol. 182 (no. 10); 1221-1227

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	No additional information
Study dates	June 2005 - October 2008
Sources of funding	Supported by GlaxoSmithKline
Inclusion criteria	Aged 6-16 years Moderate asthma with a history of bronchial hyperresponsiveness

	Receiving ICS at a maximum dose of 250 mcg per day (fluticasone equiv.) Symptomatic (cumulative symptom score (based on coughing, wheezing, shortness of breath, with a maximum daily score of 18) ≥14 over the last two weeks) during four-week run-in on 200 mcg fluticasone propionate, twice daily. Those children still symptomatic despite regular use of FP, 100mg twice a day after the 4-week run-in period were randomised to interventions.
Exclusion criteria	None reported
Recruitment / selection of participants	No additional information
Intervention(s)	Following a four-week run-in where participants received 100 mcg fluticasone propionate (dry powder) twice daily, those randomised to the ICS/LABA arm received: 50/100 mcg salmeterol/fluticasone propionate twice daily plus salbutamol (200µg Diskus) as-needed for symptom relief
Population subgroups	Exacerbations No - ~70% of participants had zero courses of oral corticosteroids in the past year Atopy Yes - ~60% of participants were atopic
Comparator	Following a four-week run-in where participants received 100 mcg fluticasone propionate twice daily, those randomised to the ICS arm received 200 mcg fluticasone propionate twice daily plus salbutamol as-needed for symptom relief
Number of participants	158 randomised 78 received ICS/LABA, 72 completed 80 received ICS monotherapy, 79 completed

Duration of follow-up	26 weeks
Indirectness	None
Additional comments	ITT and per protocol

Study arms

Regular paediatric moderate dose ICS/LABA with SABA prn (N = 78)
50/100 mcg salmeterol/fluticasone propionate, twice daily

Regular paediatric high dose ICS with SABA prn (N = 80)
200 mcg fluticasone propionate, twice daily

Characteristics

Arm-level characteristics

Characteristic	Regular paediatric moderate dose ICS/LABA with SABA prn (N = 78)	Regular paediatric high dose ICS with SABA prn (N = 80)
% Female Sample size	n = 36 ; % = 46	n = 31 ; % = 39
Mean age (SD) Mean (SD)	9.4 (1.8)	9.3 (1.9)
White Sample size	n = 70 ; % = 90	n = 73 ; % = 91
Asian	n = 1 ; % = 1	n = 2 ; % = 3

Characteristic	Regular paediatric moderate dose ICS/LABA with SABA prn (N = 78)	Regular paediatric high dose ICS with SABA prn (N = 80)
Sample size		
Black Sample size	n = 3 ; % = 4	n = 1 ; % = 1
Mixed Sample size	n = 4 ; % = 5	n = 4 ; % = 5
Comorbidities Nominal	NR	NR
ICS dose (µg/day) Nominal	NR	NR
Asthma control (%) Median (range) symptom free days during last 2 weeks of run-in Nominal	13	15
Asthma control (%) Median (range) symptom free days during last 2 weeks of run-in Range	0 to 90	0 to 90
Lung function (% of predicted) FEV1 Mean (SD)	99.4 (15.1)	100.7 (13.9)

Outcomes

Study timepoints

- Baseline
- 26 week

Continuous Outcomes

Outcome	Regular paediatric moderate dose ICS/LABA with SABA prn, Baseline, N = 78	Regular paediatric moderate dose ICS/LABA with SABA prn, 26 week, N = 78	Regular paediatric high dose ICS with SABA prn, Baseline, N = 80	Regular paediatric high dose ICS with SABA prn, 26 week, N = 80
Lung Function (FEV1) (% of predicted) FInal values Mean (SD)	99.4 (15.1)	101.8 (14.7)	100.7 (13.9)	101.5 (14.2)
Lung function (PEF) (% of predicted) Final values Mean (SD)	91.8 (16.4)	96.3 (16)	92.6 (15.1)	94.1 (15.7)

Lung Function (FEV1) - Polarity - Higher values are better
Lung function (PEF) - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	Regular paediatric moderate dose ICS/LABA with SABA prn, Baseline, N = 78	Regular paediatric moderate dose ICS/LABA with SABA prn, 26 week, N = 78	Regular paediatric high dose ICS with SABA prn, Baseline, N = 80	Regular paediatric high dose ICS with SABA prn, 26 week, N = 80
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 8 ; % = 10	n = NA ; % = NA	n = 4 ; % = 5
Adverse events Final values No of events	n = NA ; % = NA	n = 59 ; % = 76	n = NA ; % = NA	n = 62 ; % = 78

Severe asthma exacerbations - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular low dose ICS/LABA with SABA prn-Regular moderate-high dose ICS with SABA prn-t26

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-LungFunction(FEV1)-MeanSD-Regular low dose ICS/LABA with SABA prn-Regular moderate-high dose ICS with SABA prn-t26

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Lungfunction(PEF)-MeanSD-Regular low dose ICS/LABA with SABA prn-Regular moderate-high dose ICS with SABA prn-t26

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular low dose ICS/LABA with SABA prn-Regular low/moderate dose ICS with SABA prn-t26

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No information about randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

D.4 Children under 5 years

Fitzpatrick, 2016

Bibliographic Reference	Fitzpatrick, Anne M; Jackson, Daniel J; Mauger, David T; Boehmer, Susan J; Phipatanakul, Wanda; Sheehan, William J; Moy, James N; Paul, Ian M; Bacharier, Leonard B; Cabana, Michael D; Covar, Ronina; Holguin, Fernando; Lemanske, Robert F Jr; Martinez, Fernando D; Pongracic, Jacqueline A; Beigelman, Avraham; Baxi, Sachin N; Benson, Mindy; Blake, Kathryn; Chmiel, James F; Daines, Cori L; Daines, Michael O; Gaffin, Jonathan M; Gentile, Deborah Ann; Gower, W Adam; Israel, Elliot; Kumar, Harsha Vardhan; Lang, Jason E; Lazarus, Stephen C; Lima, John J; Ly, Ngoc; Marbin, Jyothi; Morgan, Wayne; Myers, Ross E; Olin, J Tod; Peters, Stephen P; Raissy, Hengameh H; Robison, Rachel G; Ross, Kristie; Sorkness, Christine A; Thyne, Shannon M; Szefler, Stanley J; Individualized therapy for persistent asthma in young children.; The Journal of allergy and clinical immunology; 2016; vol. 138 (no. 6); 1608-1618e12

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	INFANT - Individualized Therapy for Asthma in Toddlers - NCT01606306
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	No additional information
Sources of funding	Funded by NHLBI

Inclusion criteria	Aged 12-59 months Met guideline-based criteria for daily asthma medication (step-2 treatment) Receiving only intermittent bronchodilators, low-dose ICS or LTRAs Daytime symptoms on more than 2 days per week on average over the past month, night time awakening once, or four or more wheezing episodes, each lasting more than 24 hours in the previous year Two or more exacerbations in the last 6 months if not currently receiving ICS or LTRA, or two or more exacerbations in the past 12 months if receiving ICS or LTRA
Exclusion criteria	<75% symptom diary adherence during run-in Exacerbation requiring systemic steroids during run-in Daily asthma symptoms if not receiving active therapy Symptoms on more than 2 days per week if receiving active therapy
Recruitment / selection of participants	Recruited from 18 sites through a variety of methods, including advertisements, primary care and specialty care clinic referrals, and screenings of urgent care facility visits and after-hours telephone logs
Intervention(s)	Following a 2-8 week run-in period (2 weeks if history of exacerbation, up to 8 weeks to elicit symptoms if no exacerbation history in those not receiving treatment, and 4 weeks in those previously receiving ICS or LTRA) where participants received once daily open-label oral prednisolone and albuterol if currently on step-2 therapy, or placebos if treatment naïve, participants were allocated to one of three treatments: • Regular ICS - 44 mcg fluticasone propionate, two inhalations twice daily, plus placebo montelukast and ICS/SABA

	• As-needed ICS/SABA - 44 mcg fluticasone propionate plus 90 mcg salbutamol, two inhalations of each as-needed for symptom relief, plus placebo montelukast and regular ICS • Regular montelukast - 4 mg montelukast once daily in the evening, plus placebo regular ICS and as-needed ICS/SABA Participants received treatment for 16 weeks per study arm with no washout between treatments Integrated within this crossover study was a parallel study comparing acetaminophen with ibuprofen (NCT01606319). Whilst switching between asthma therapies, participants maintained their background treatment.
Population subgroups	**Exacerbations** Mixed - 75% with an exacerbation in past year **Atopy** Mixed - 43.5% with one positive aeroallergen, 54.8% with eczema
Comparator	See interventions
Number of participants	300 randomised 230 with data able to evaluated 226 completed all three periods
Duration of follow-up	16 weeks per treatment, 48 weeks total
Indirectness	None

Additional comments	Available case analysis

Study arms

Regular ICS (N = 230)
44 mcg fluticasone propionate, two inhalations twice daily

As-needed ICS/SABA (N = 230)
44 mcg fluticasone propionate plus 90 mcg salbutamol, both two inhalations as-needed

Regular montelukast (N = 230)
4 mg montelukast once daily in the evening

Characteristics

Study-level characteristics

Characteristic	Study (N = 230)
% Female Sample size	n = 87 ; % = 38
Mean age (SD) Months Mean (SD)	39.7 (13)
African American Sample size	n = 66 ; % = 29
White	n = 120 ; % = 52

Characteristic	Study (N = 230)
Sample size	
Hispanic Sample size	n = 56 ; % = 24
Comorbidities Nominal	NR
ICS Sample size	n = 149 ; % = 65
LTRA Sample size	n = 15 ; % = 7

Outcomes

Study timepoints

- Baseline
- 16 week

Dichotomous Outcomes

Outcome	Regular ICS, Baseline, N = 300	Regular ICS, 16 week, N = 249	As-needed ICS/SABA , Baseline, N = 300	As-needed ICS/SABA , 16 week, N = 250	Regular montelukast, Baseline, N = 300	Regular montelukast, 16 week, N = 256
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 47 ; % = 19	n = NA ; % = NA	n = 69 ; % = 28	n = NA ; % = NA	n = 87 ; % = 34
Hospital admissions Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 6 ; % = 2
Pneumonia Final values No of events	n = NA ; % = NA	n = 1 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Severe asthma exacerbations - Polarity - Lower values are better
Hospital admissions - Polarity - Lower values are better
Pneumonia - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular ICS-As-needed ICS/SABA -Regular montelukast-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and 23% missing outcome data with no reasons for discontinuation reported)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Hospitaladmissions-NoOfEvents-Regular ICS-As-needed ICS/SABA -Regular montelukast-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and 23% missing outcome data with no reasons for discontinuation reported)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia-NoOfEvents-Regular ICS-As-needed ICS/SABA -Regular montelukast-t16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported and 23% missing outcome data with no reasons for discontinuation reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Szefler, 2013

Bibliographic Reference	Szefler, Stanley J; Carlsson, Lars-Goran; Uryniak, Tom; Baker, James W; Budesonide inhalation suspension versus montelukast in children aged 2 to 4 years with mild persistent asthma.; The journal of allergy and clinical immunology. In practice; 2013; vol. 1 (no. 1); 58-64

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	NCT00641472
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	October 2002 - February 2005
Sources of funding	Funded by AstraZeneca
Inclusion criteria	Children aged 2-4 years (subgroup analysis of 2-8 year olds included in primary trial) Symptoms of mild persistent asthma or had ≥3 wheezing episodes that lasted more than 1-day and affected sleep Cumulative asthma symptom score ≥2 and used SABA on ≥3 of 7 consecutive days during the run-in period

Exclusion criteria	History of severe or unstable asthma Hypersensitivity to study medications Past or present significant disease Acute asthma exacerbation or respiratory tract infection within 30 days Used montelukast or ICS within 1-week, systemic corticosteroids within 2 weeks or omalizumab within 6 months
Recruitment / selection of participants	Recruited from 55 centres, method not reported
Intervention(s)	Following a 3-21-day run-in period where participants could not receive orally administered albuterol, leukotriene modifiers, inhaled long-acting b2-adrenergic agonists, systemic corticosteroids or ICSs, inhaled anticholinergic medications, or omalizumab, participants were allocated to one of two treatment options: • 500 mcg budesonide once daily in the evening • 4 mg montelukast taken once daily in the evening
Population subgroups	**Exacerbations** Not reported **Atopy** Not reported
Comparator	See interventions

Number of participants	203 randomised 105 allocated to ICS, 74 completed 97 allocated to montelukast, 72 completed
Duration of follow-up	52 weeks
Indirectness	None
Additional comments	ITT

Study arms

Regular ICS (N = 105)

500 mcg budesonide once daily

Regular montelukast (N = 97)

4 mg montelukast once daily

Characteristics

Arm-level characteristics

Characteristic	Regular ICS (N = 105)	Regular montelukast (N = 97)
% Female Sample size	n = 34 ; % = 32	n = 37 ; % = 38
Mean age (SD) Mean (SD)	3.04 (0.87)	3.03 (0.85)

Characteristic	Regular ICS (N = 105)	Regular montelukast (N = 97)
White Sample size	n = 86 ; % = 82	n = 82 ; % = 85
Black Sample size	n = 15 ; % = 14	n = 14 ; % = 14
Asian Sample size	n = 2 ; % = 2	n = 1 ; % = 1
Other Sample size	n = 2 ; % = 2	n = 0 ; % = 0
Comorbidities Nominal	NR	NR
Asthma control (Puffs per day) SABA use Mean (SD)	1.61 (1.23)	1.63 (1.13)
Lung function (L/min) Morning PEF Mean (SD)	89.8 (30.4)	91.9 (32.3)
ICS Sample size	n = 8 ; % = 8	n = 7 ; % = 7
LTRA	n = 1 ; % = 1	n = 0 ; % = 0

Characteristic	Regular ICS (N = 105)	Regular montelukast (N = 97)
Sample size		

Outcomes

Study timepoints

- Baseline
- 52 week
- 12 week

Continuous Outcomes

Outcome	Regular ICS, Baseline, N = 105	Regular ICS, 52 week, N = 74	Regular ICS, 12 week, N = 105	Regular montelukast, Baseline, N = 97	Regular montelukast, 52 week, N = 72	Regular montelukast, 12 week, N = 105
Lung function (PEF) (Litres per minute) Change scores Mean (SD)	NA (NA)	NR (NR)	21.1 (23.6)	NA (NA)	NR (NR)	14 (22.7)
Reliever/rescue medication use (Puffs per day) Change scores Mean (SD)	NA (NA)	NR (NR)	-0.69 (1.13)	NA (NA)	NR (NR)	-0.72 (1.08)

Lung function (PEF) - Polarity - Higher values are better
Reliever/rescue medication use - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Regular ICS, Baseline, N = 105	Regular ICS, 52 week, N = 74	Regular ICS, 12 week, N = 105	Regular montelukast, Baseline, N = 97	Regular montelukast, 52 week, N = 72	Regular montelukast, 12 week, N = 97
Severe asthma exacerbations Final values No of events	n = NA ; % = NA	n = 23 ; % = 21.9	n = NR ; % = NR	n = NA ; % = NA	n = 36 ; % = 37.1	n = NR ; % = NR
Mortality Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NR ; % = NR	n = NA ; % = NA	n = 0 ; % = 0	n = NR ; % = NR
Adverse events Final values No of events	n = NA ; % = NA	n = 84 ; % = 80	n = NR ; % = NR	n = NA ; % = NA	n = 80 ; % = 82	n = NR ; % = NR
Pneumonia Final values No of events	n = NA ; % = NA	n = 4 ; % = 4	n = NR ; % = NR	n = NA ; % = NA	n = 6 ; % = 6	n = NR ; % = NR

Severe asthma exacerbations - Polarity - Lower values are better
Mortality - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better
Pneumonia - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
ContinuousOutcomes-Lungfunction(PEF)-MeanSD-Regular ICS-Regular montelukast-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 8% difference in additional medication received between study arms and 28% dropout rate with reasons for discontinuation that could have been related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

ContinuousOutcomes-Reliever/rescuemedicationuse-MeanSD-Regular ICS-Regular montelukast-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 8% difference in additional medication received between study arms and 28% dropout rate with reasons for discontinuation that could have been related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Pneumonia-NoOfEvents-Regular ICS-Regular montelukast-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 8% difference in additional medication received between study arms and 28% dropout rate with reasons for discontinuation that could have been related to participant's health status)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Adverseevents-NoOfEvents-Regular ICS-Regular montelukast-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 8% difference in additional medication received between study arms and 28% dropout rate with reasons for discontinuation that could have been related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Mortality-NoOfEvents-Regular ICS-Regular montelukast-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 8% difference in additional medication received between study arms and 28% dropout rate with reasons for discontinuation that could have been related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

DichotomousOutcomes-Severeasthmaexacerbations-NoOfEvents-Regular ICS-Regular montelukast-t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation method not reported, 8% difference in additional medication received between study arms and 28% dropout rate with reasons for discontinuation that could have been related to participant's health status)*
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plots

E.1 First add-on treatment for adults and young people ≥12 years with uncontrolled asthma

Regular low dose ICS/LABA with SABA prn vs regular low dose ICS with SABA prn

Figure 2: Severe asthma exacerbations at 3-5 months (final values, lower is better)

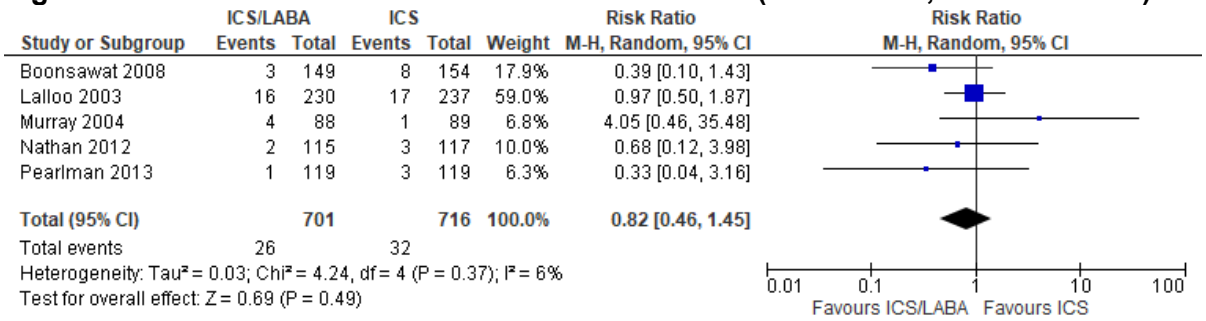


Figure 3: Severe asthma exacerbations at ≥6 months (final values, lower is better)

Figure 4: Severe exacerbation rate (final values, lower is better)

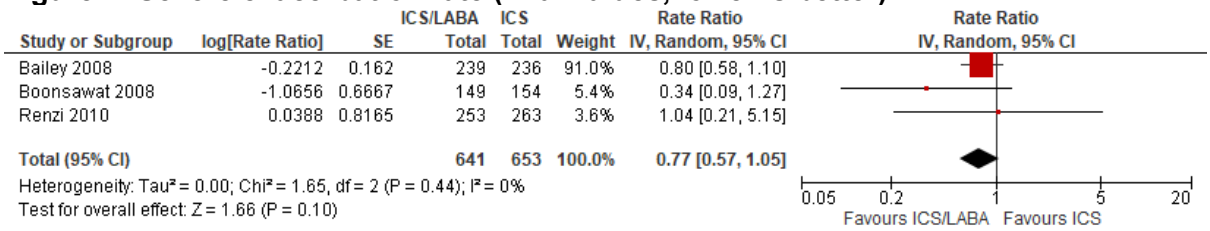


Figure 5: Mortality (final values, lower is better)

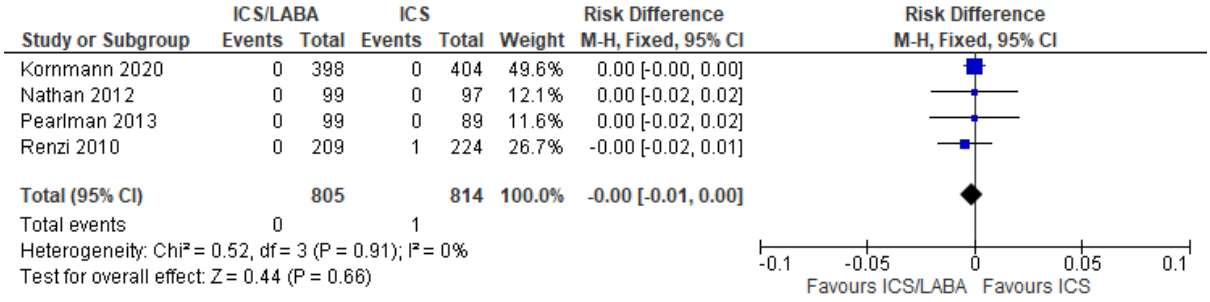


Figure 6: Asthma control (Asthma Control Questionnaire-7, scale range 0-6, change scores, lower is better)

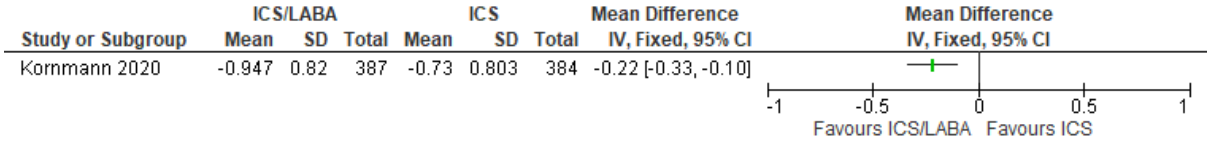


Figure 7: Hospital admissions at 3-5 months (final values, lower is better)

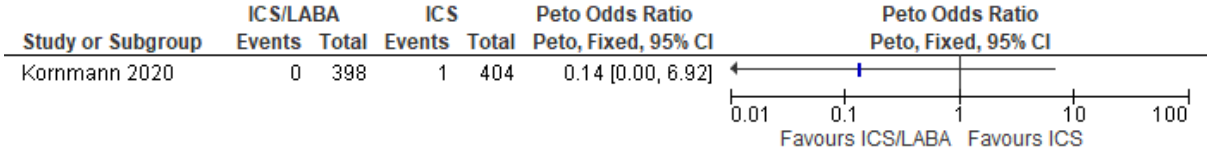


Figure 8: Hospital admissions at ≥6 months (final values, lower is better)

Figure 9: Reliever/rescue medication use (puffs per day, change scores, lower is better)

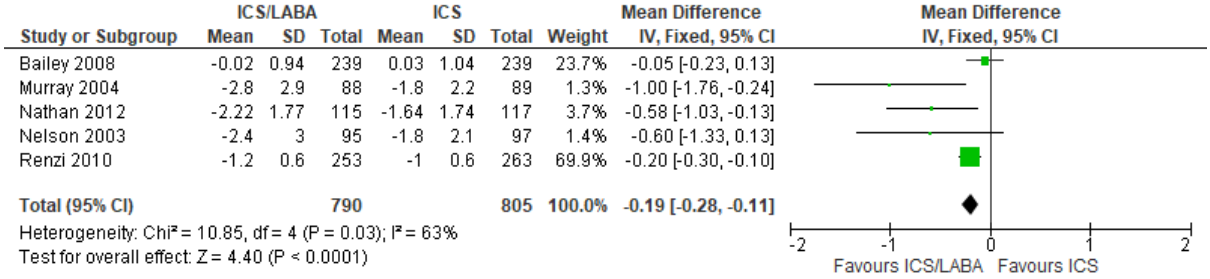


Figure 10: Reliever/rescue medication use (% SABA-free days, mixed values, higher is better)

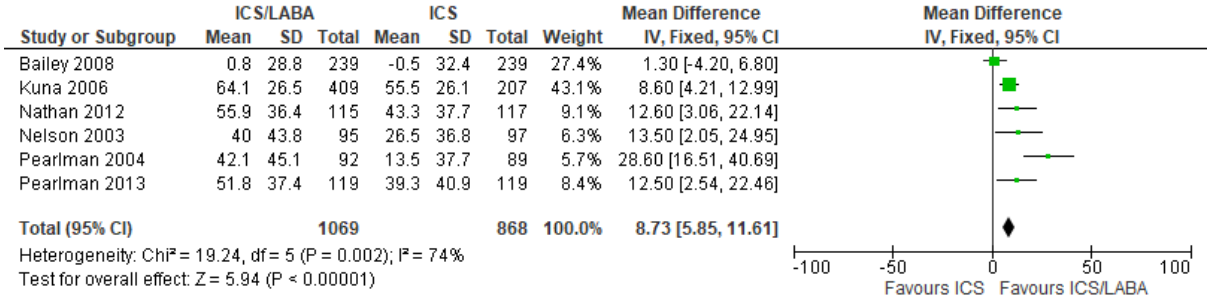


Figure 11: Lung function (FEV_1, litres, change scores, higher is better)

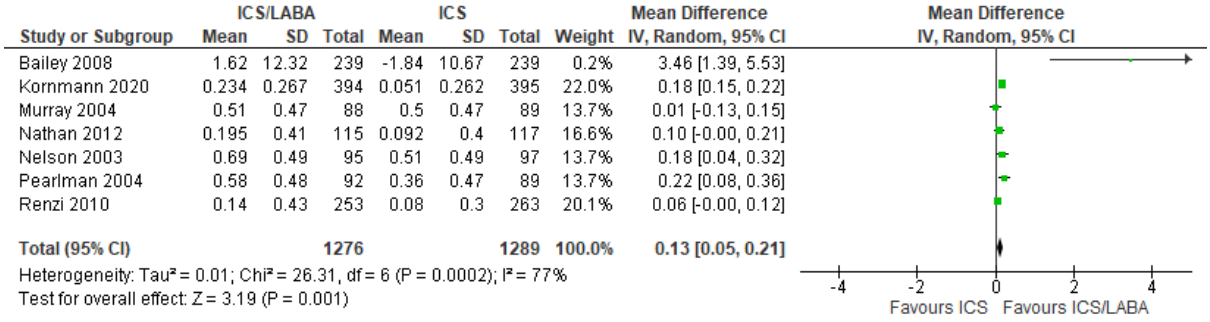


Figure 12: Lung function (PEF, L/min, change scores, higher is better)

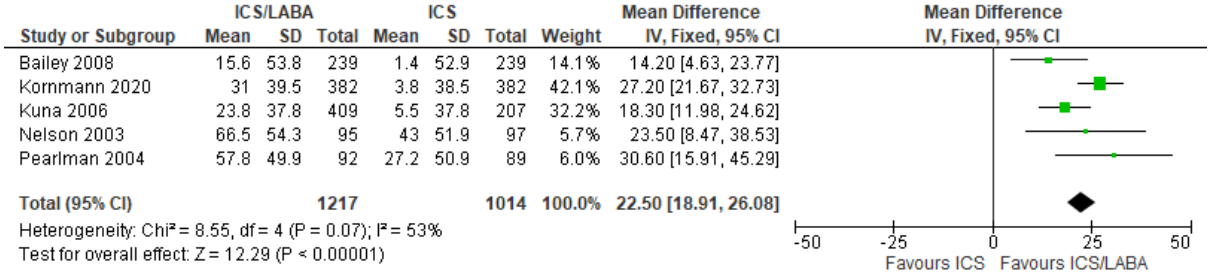


Figure 13: Lung function (PEF, % of predicted, change scores, higher is better)

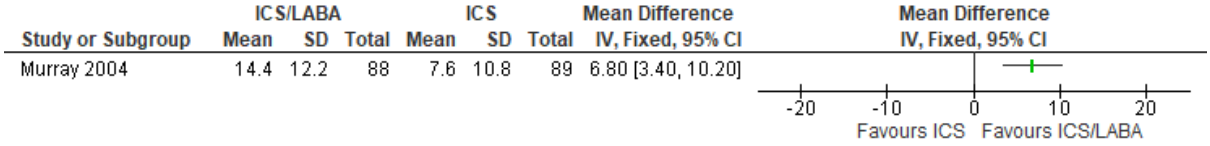


Figure 14: Adverse events (final values, lower is better)

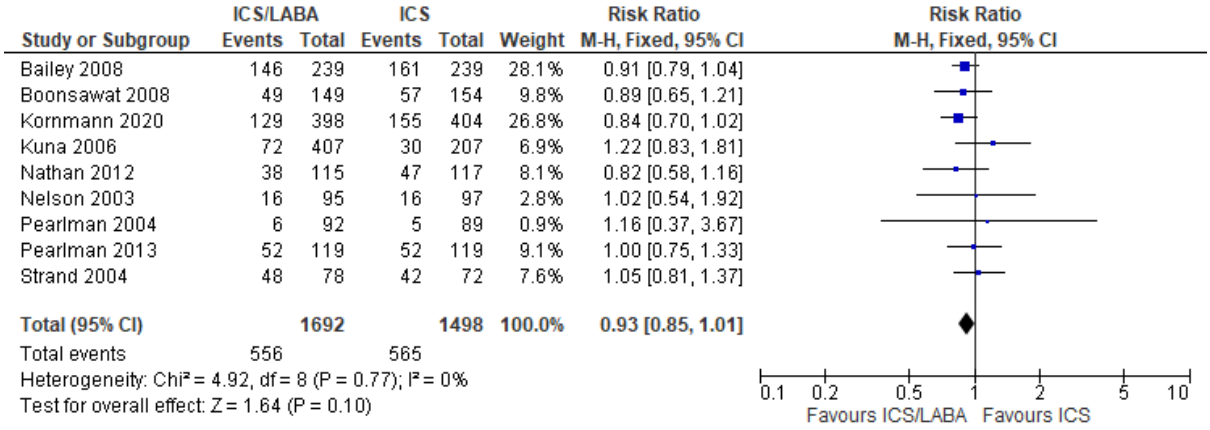
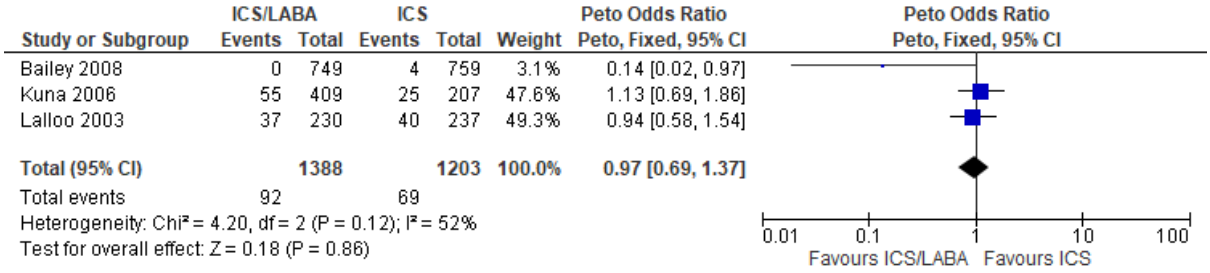


Figure 15: Pneumonia (respiratory tract infections, final values, lower is better)



Low dose ICS/formoterol MART vs regular low dose ICS with SABA prn

Figure 16: Severe asthma exacerbations at ≥6 months (final values, lower is better)

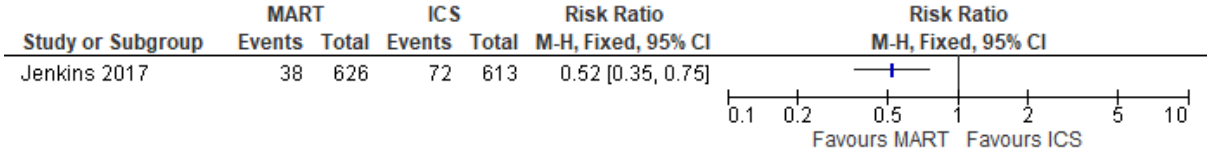


Figure 17: Severe exacerbation rate (final values, lower is better)

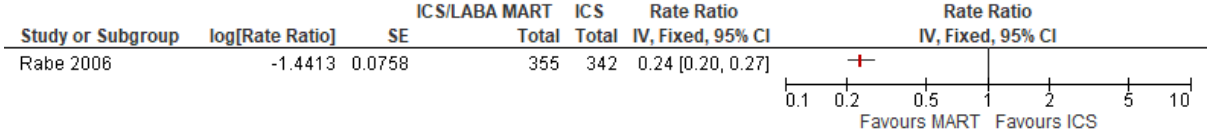


Figure 18: Hospital admissions at ≥6 months (final values, lower is better)

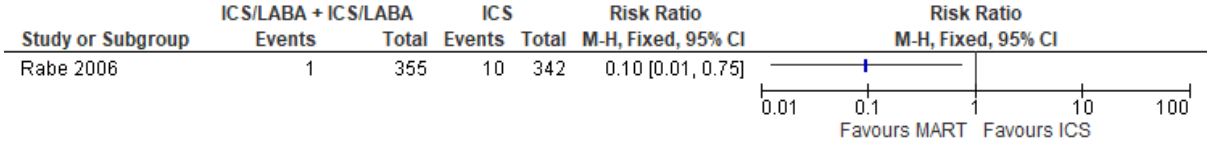


Figure 19: Reliever/rescue mediation use (puffs per day, change scores, lower is better)

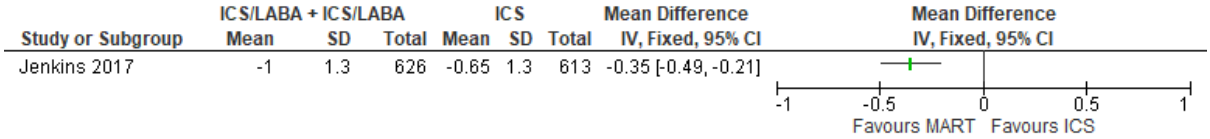


Figure 20: Reliever/rescue medication use (reliever-free days, %, final values, higher is better)

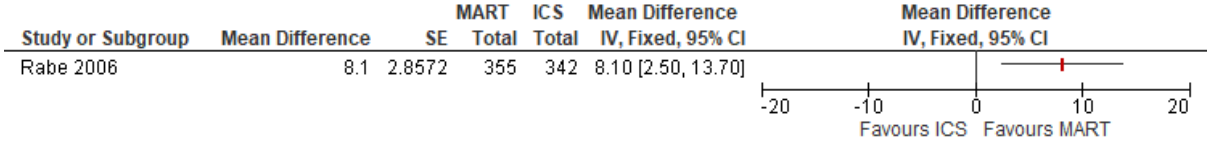


Figure 21: Lung function (FEV_1, litres, change scores, higher is better)

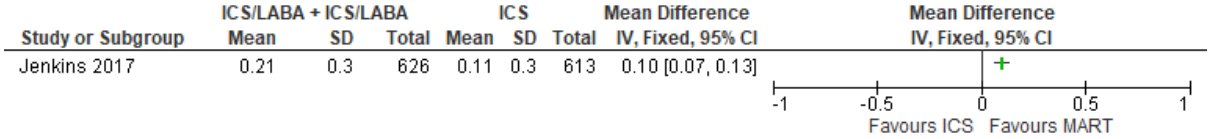


Figure 22: Lung function (PEF, L/minute, final values, higher is better)

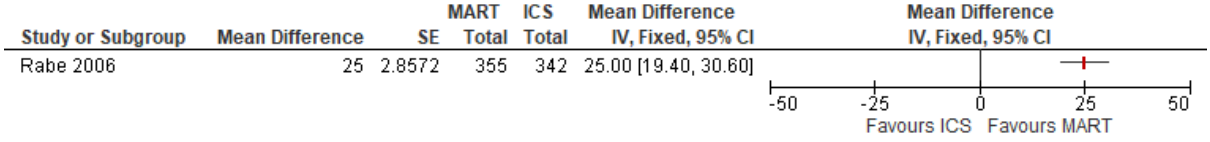


Figure 23: Adverse events (final values, lower is better)

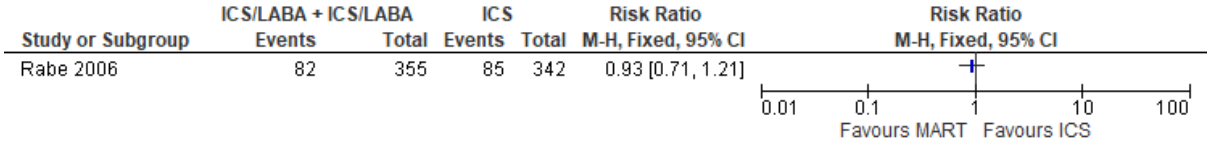
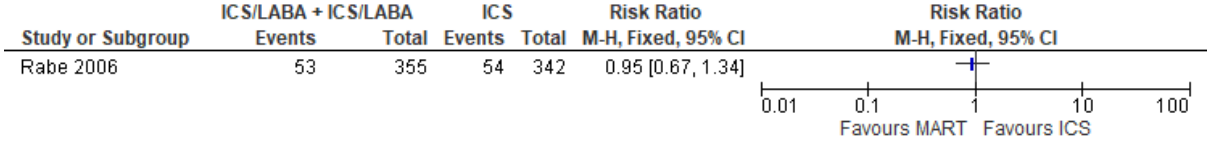


Figure 24: Pneumonia (respiratory tract infections, final values, lower is better)



Low dose ICS/formoterol MART vs regular low dose ICS/LABA with SABA prn

Figure 25: Severe asthma exacerbations at ≥6 months (final values, lower is better)

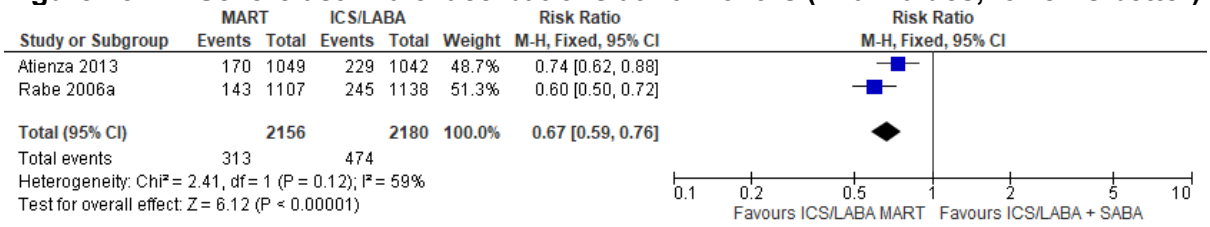


Figure 26: Severe exacerbation rate (final values, lower is better)

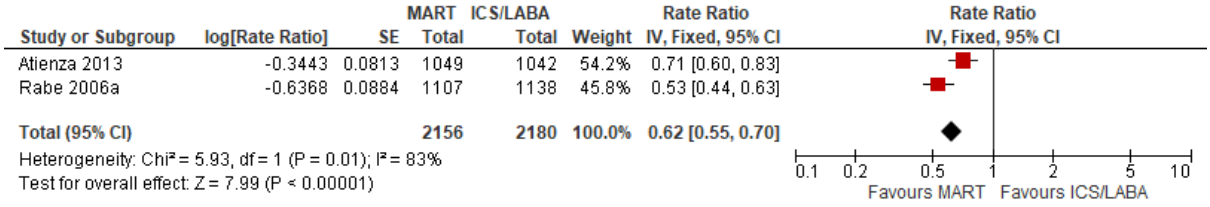


Figure 27: Mortality (final values, lower is better)

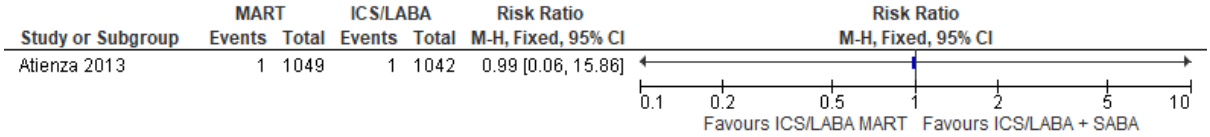


Figure 28: Asthma control (Asthma Control Questionnaire, scale range: 0-6, final values, lower is better)

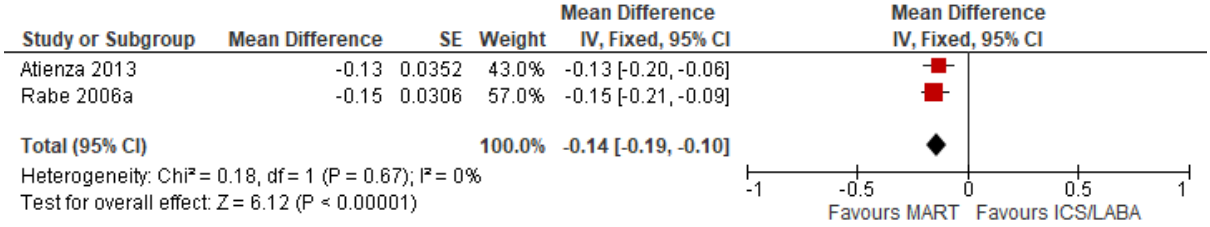


Figure 29: Hospital admissions at ≥6 months (final values, lower is better)

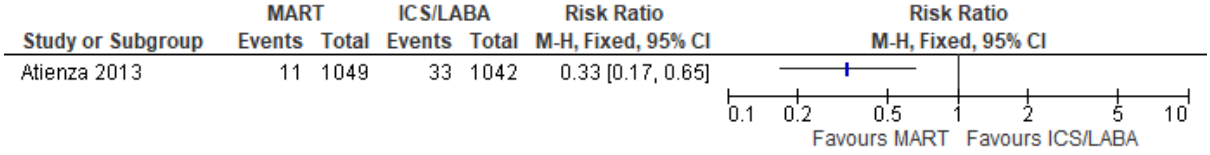


Figure 30: Reliever/rescue medication use (puffs per day, change scores, lower is better)

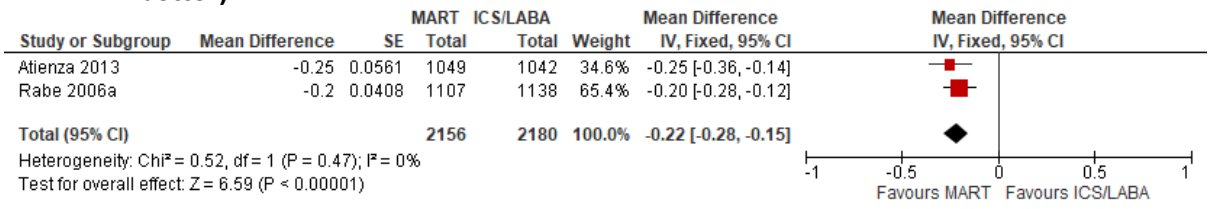


Figure 31: Reliever/rescue medication use (reliever-free days, %, change scores, high is better)

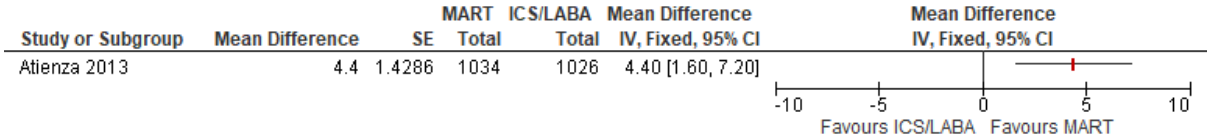


Figure 32: Lung function (FEV_1, litres, change scores, higher is better)

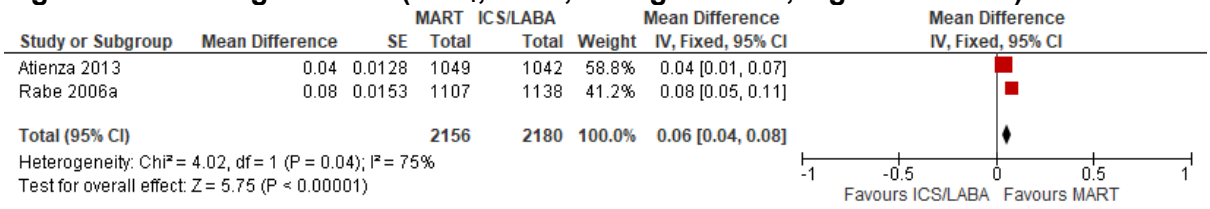


Figure 33: Lung function (PEF, litres per minute, change scores, higher is better)

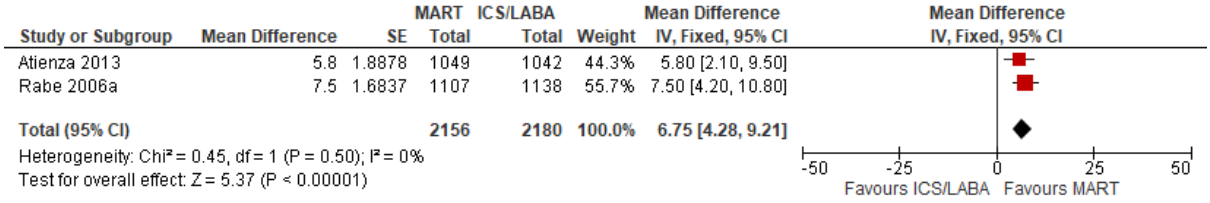
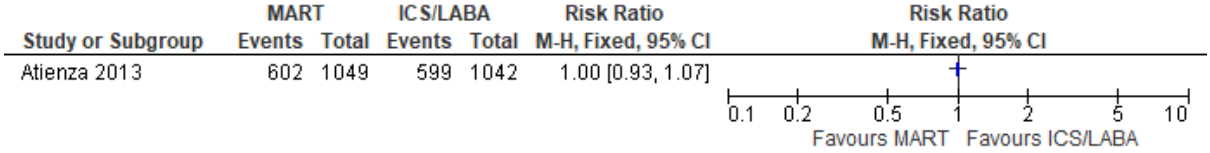


Figure 34: Adverse events (final values, lower is better)



E.2 Further step-up treatment for adults and young people ≥12 years with uncontrolled asthma

ICS/formoterol MART vs regular moderate/high dose ICS/LABA with SABA prn

Figure 35: Severe asthma exacerbations at ≥6 months (final values, lower is better)

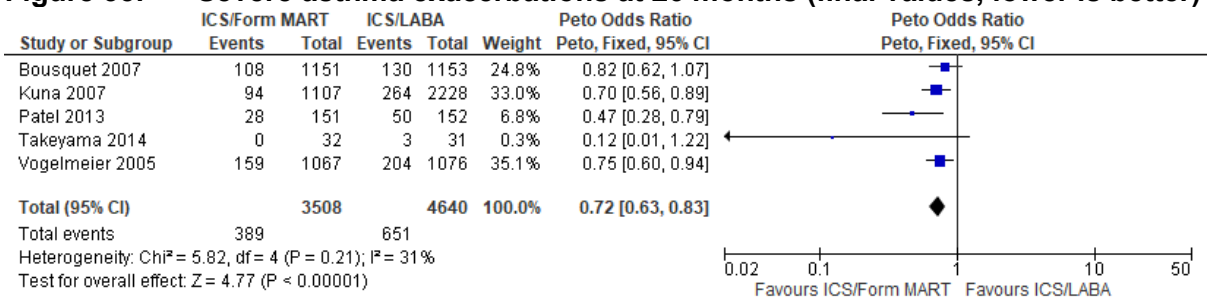


Figure 36: Severe exacerbation rate (rate per person year, final values, lower is better)

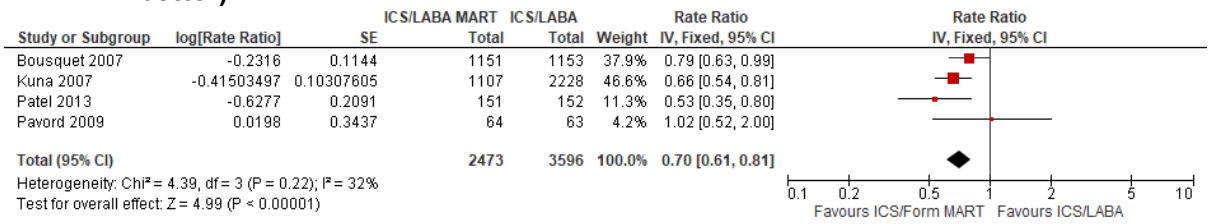


Figure 37: Mortality (final values, lower is better)

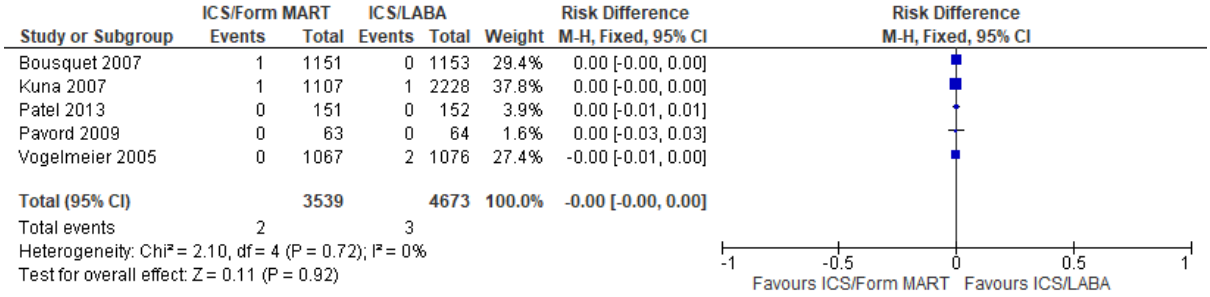


Figure 38: Quality of life (Asthma Quality of Life Questionnaire with standard activities, scale range: 1-7, change scores, higher is better)

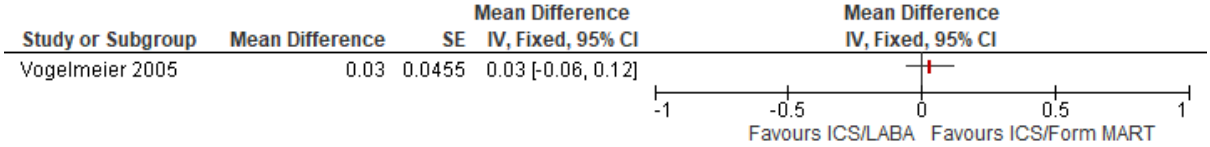


Figure 39: Asthma control (Asthma Control Questionnaire, scale range: 1-6, final values, lower is better)

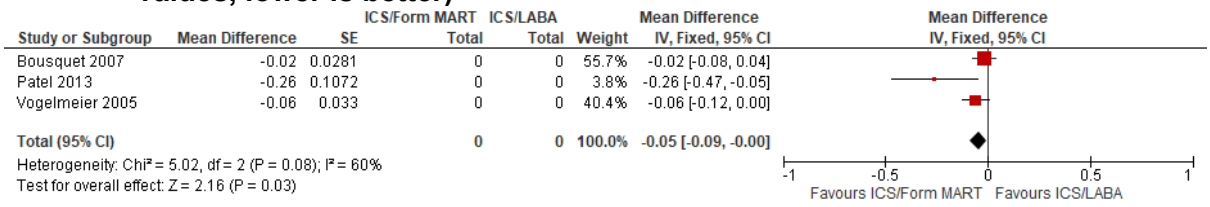


Figure 40: Hospital admissions at ≥6 months (final values, lower is better)

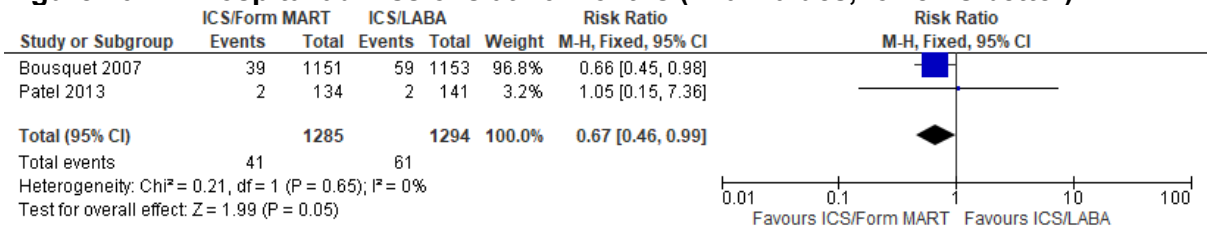


Figure 41: Reliever/rescue medication use (puffs per day, final values, lower is better)

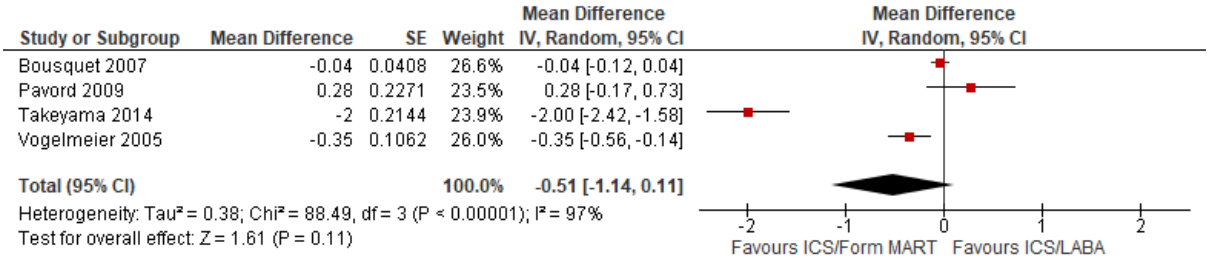


Figure 42: Lung function (FEV_1, litres, change scores, higher is better)

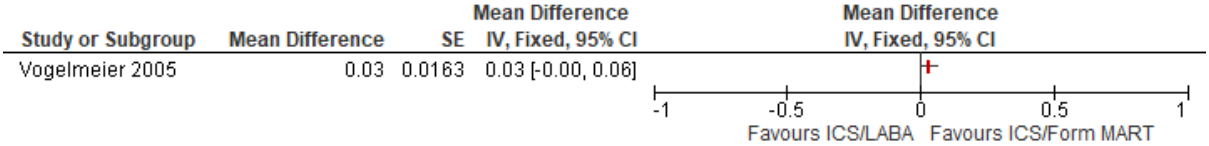


Figure 43: Lung function (FEV_1, % of predicted, final values, higher is better)

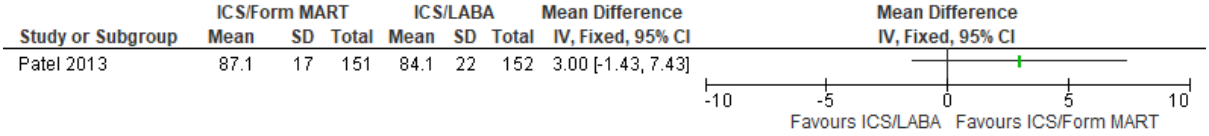


Figure 44: Lung function (PEF, litres per minute, final values, higher is better)

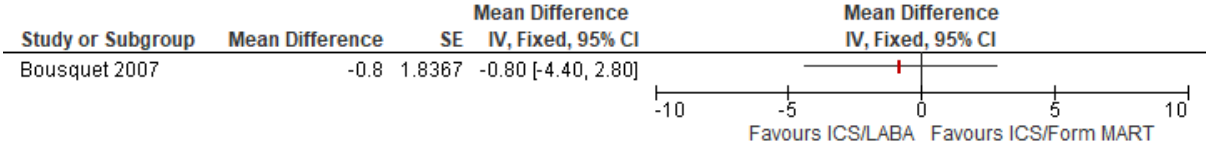


Figure 45: Adverse events (final values, lower is better)

ICS/formoterol MART vs regular moderate/high dose ICS with SABA prn

Figure 46: Severe asthma exacerbations at ≥6 months (final values, lower is better)

Figure 47: Severe exacerbation rate (rate per person year, final values, lower is better)

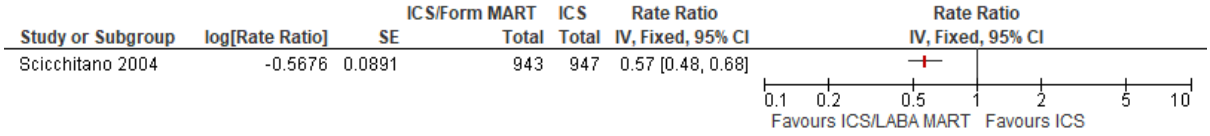


Figure 48: Mortality (final values, lower is better)

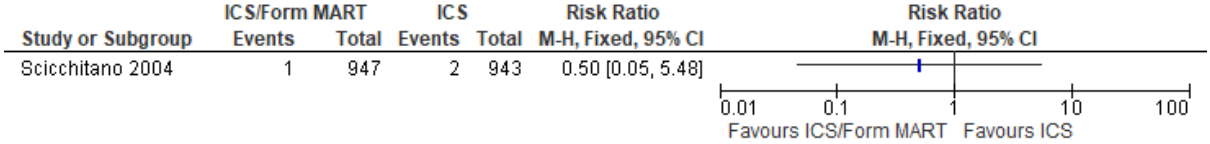


Figure 49: Reliever/rescue medication use (nighttime reliever use, puffs per night, final values, lower is better)

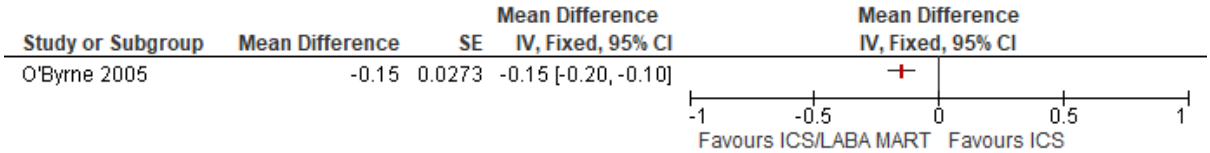


Figure 50: Reliever/rescue medication use (daytime reliever use, puffs per day, final values, lower is better)

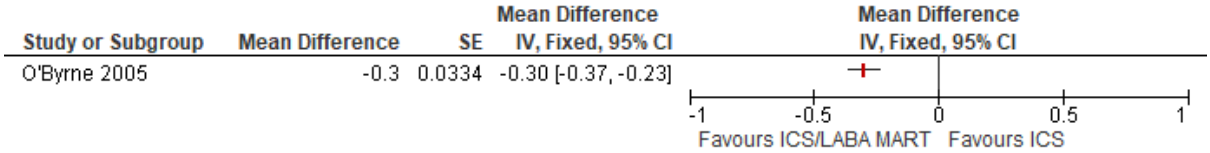


Figure 51: Reliever/rescue medication use (% reliever-free days, change scores, higher is better)

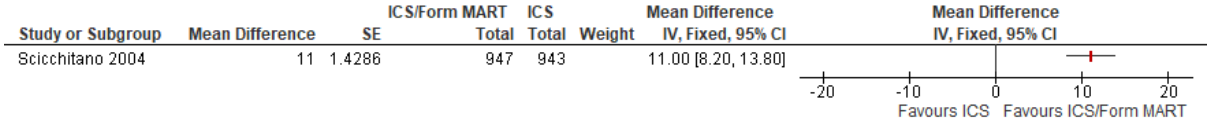


Figure 52: Lung function (FEV_1, litres, change scores, higher is better)

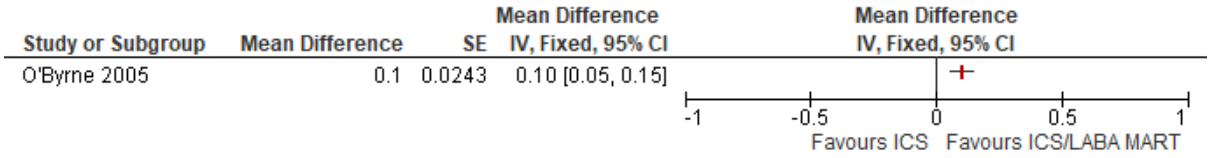


Figure 53: Lung function (PEF, L/min, change scores, higher is better)

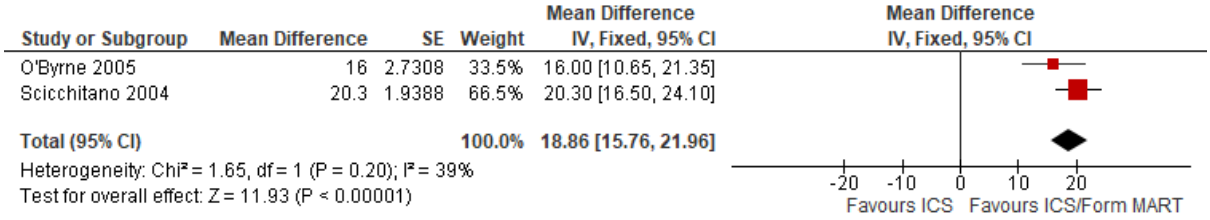


Figure 54: Adverse events (final values, lower is better)

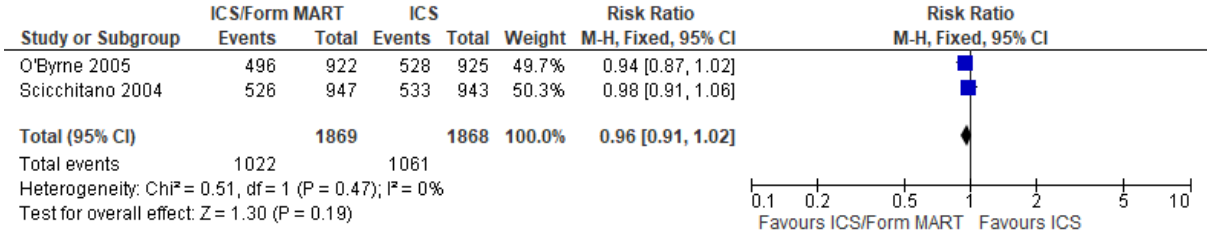
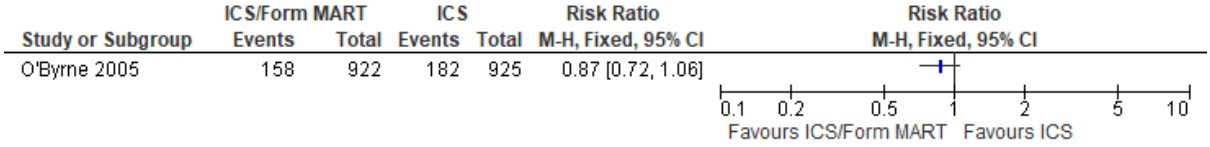


Figure 55: Pneumonia (final values, lower is better)



Regular moderate/high dose ICS/LABA with SABA prn vs regular low/moderate dose ICS/LABA + montelukast with SABA prn

Figure 56: Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)

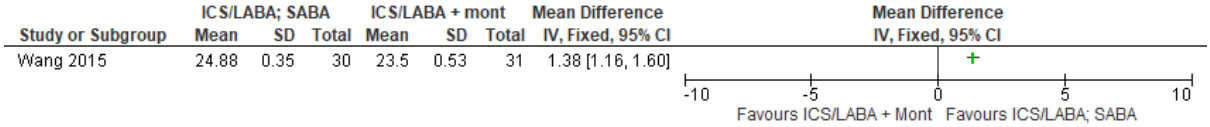
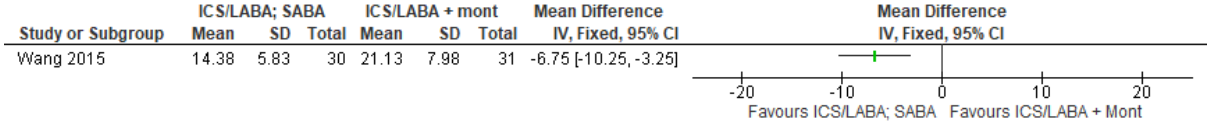


Figure 57: Inflammatory markers (FeNO, ppb, final values, lower is better)



Regular low/moderate dose ICS/LABA plus LAMA with SABA prn vs regular moderate/high dose ICS/LABA with SABA prn

Figure 58: Severe asthma exacerbations at ≥6 months (final values, lower is better)

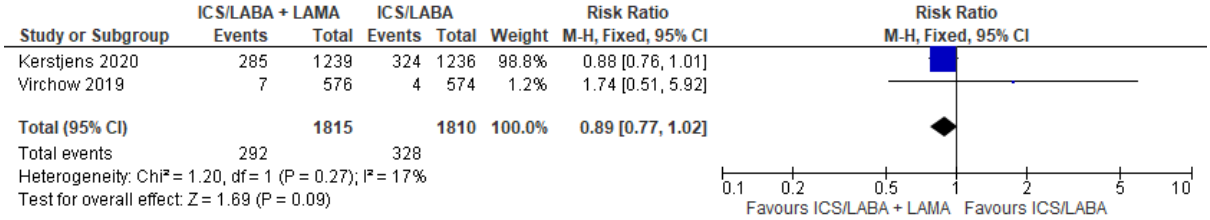


Figure 59: Mortality (final values, lower is better)

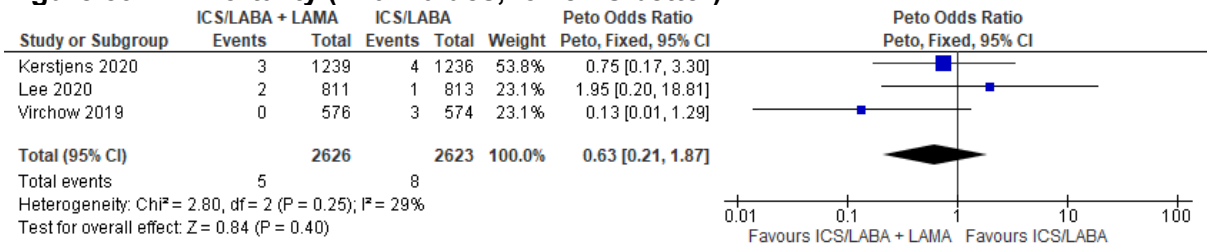


Figure 60: Quality of life (Asthma Quality of Life Questionnaire, scale range 1-7, change scores, higher is better)

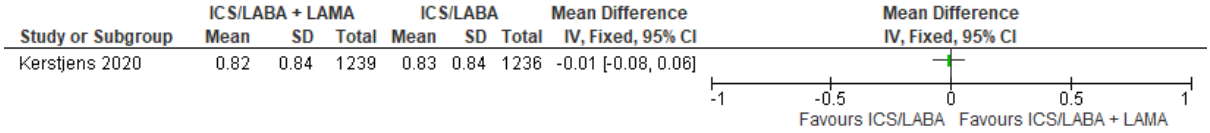


Figure 61: Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)

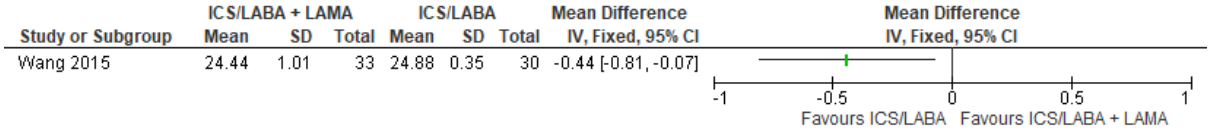


Figure 62: Reliever/rescue medication use (puffs per day, change scores, lower is better)

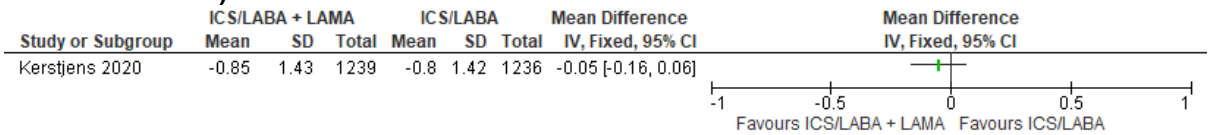


Figure 63: Reliever/rescue medication use (SABA-free days, %, change scores, higher is better)

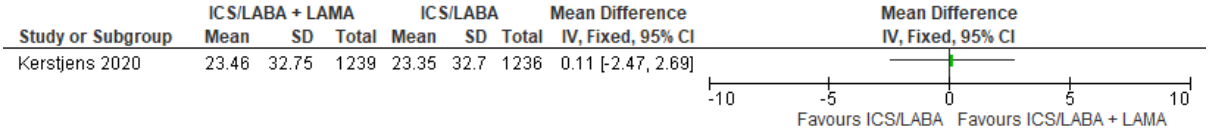


Figure 64: Lung function (FEV_1, mL, change scores, higher is better)

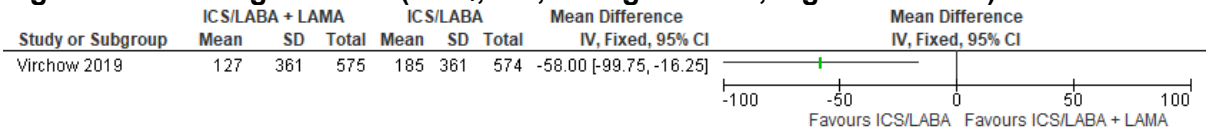


Figure 65: Lung function (PEF, L/min, change scores, higher is better)

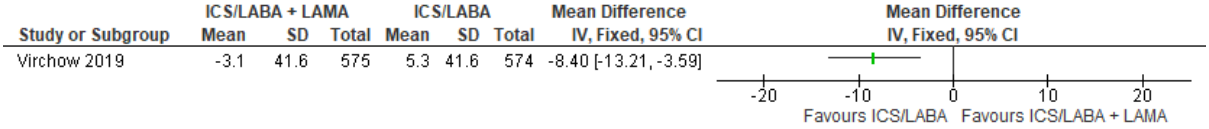


Figure 66: Adverse events (final values, lower is better)

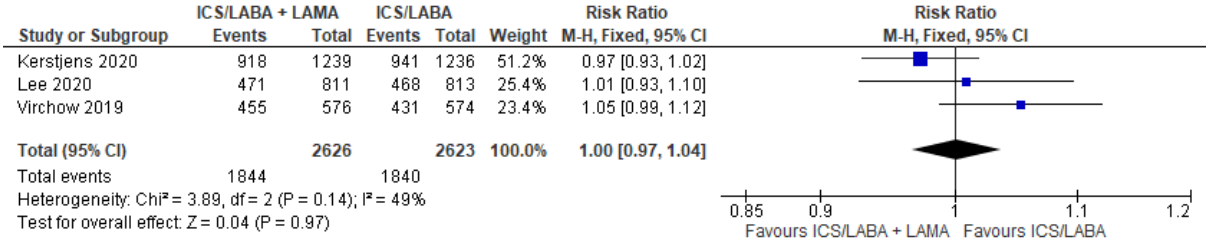


Figure 67: Pneumonia (final values, lower is better)

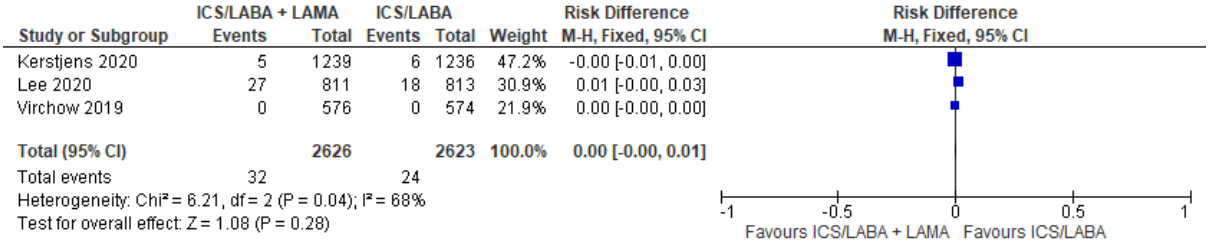
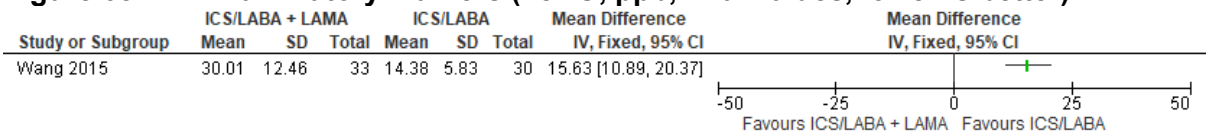


Figure 68: Inflammatory markers (FeNO, ppb, final values, lower is better)



Regular moderate/high dose ICS/LABA with SABA prn vs regular moderate/high dose ICS with SABA prn

Figure 69: Severe asthma exacerbations at 3-5 months (final values, lower is better)

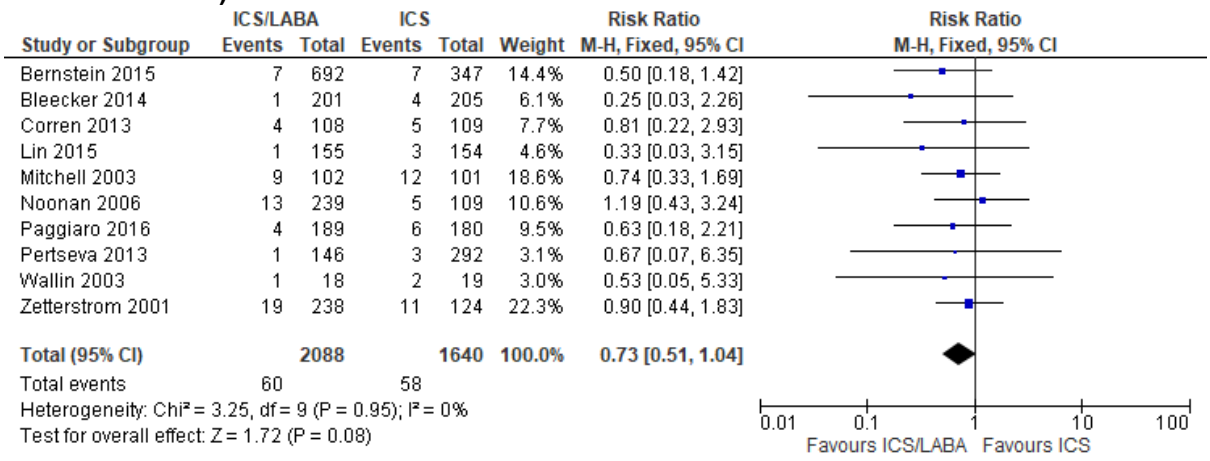


Figure 70: Severe asthma exacerbations at ≥6 months (final values, lower is better)

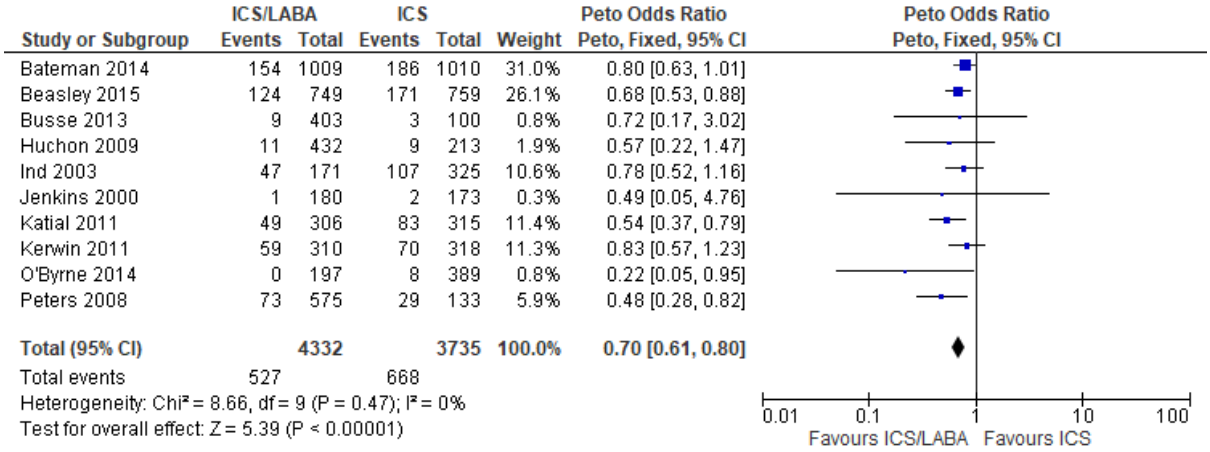


Figure 71: Severe exacerbation rate (rate per person year, final values, lower is better)

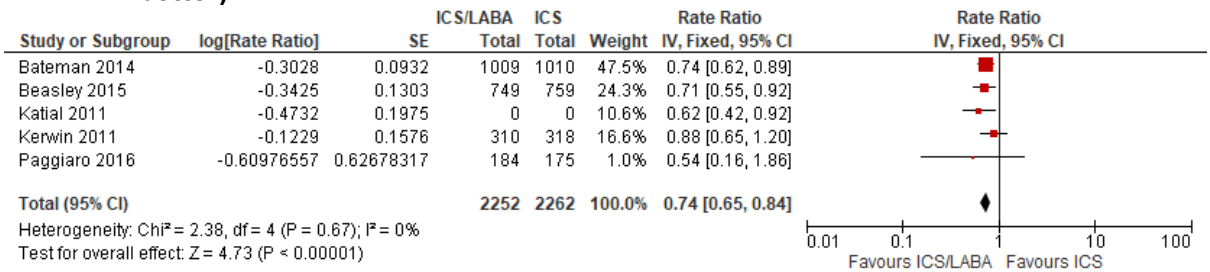


Figure 72: Mortality (final values, lower is better)

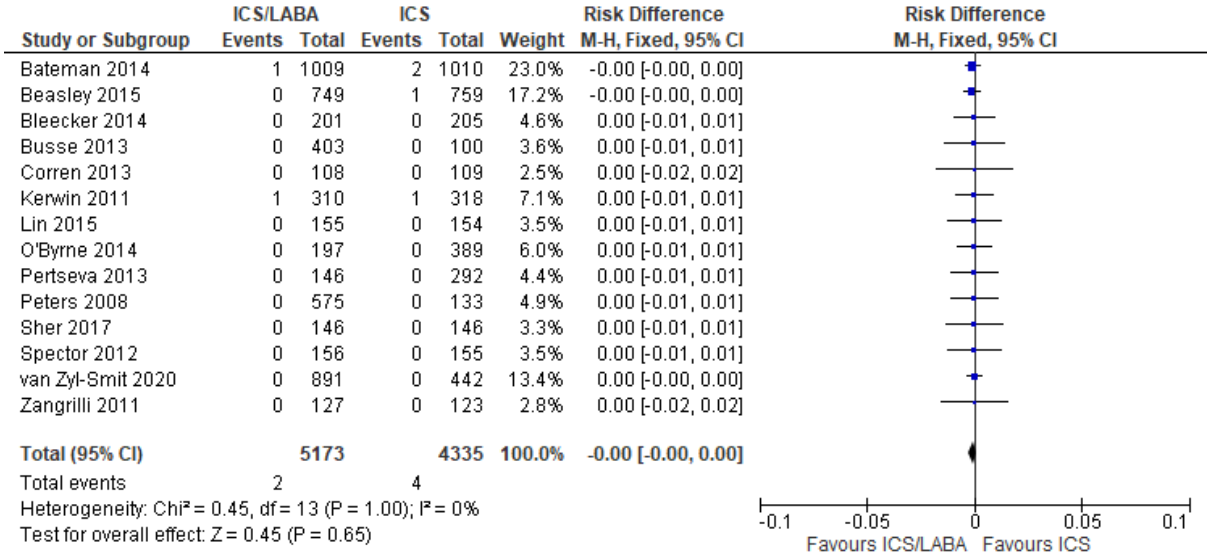


Figure 73: Quality of life (Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)

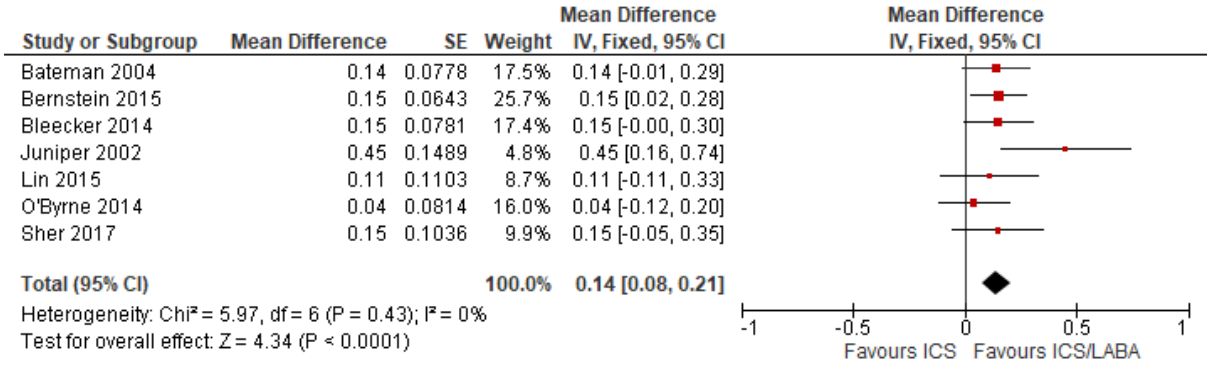


Figure 74: Asthma control (Asthma Control Test, scale range: 5-25, mixed values, higher is better)

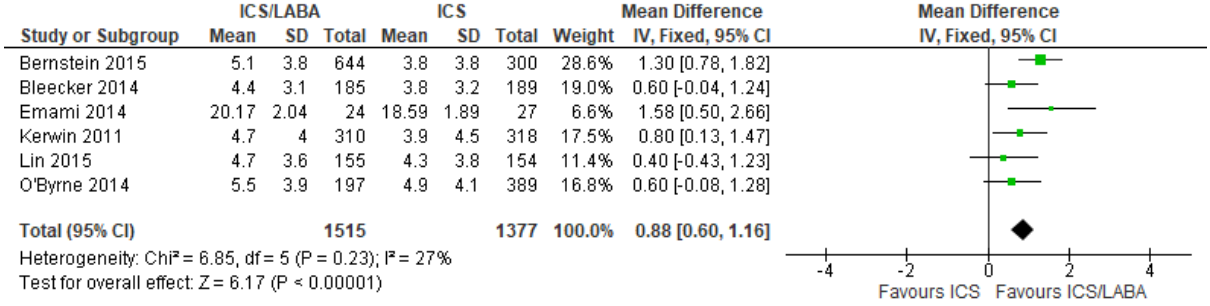


Figure 75: Asthma control (Asthma control questionnaire-7, scale range: 0-6, change scores, lower is better)

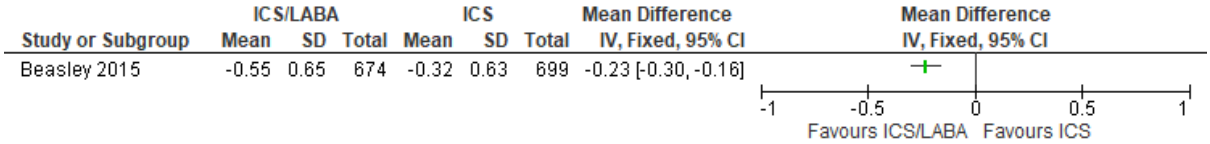


Figure 76: Hospital admissions at ≥6 months (final values, lower is better)

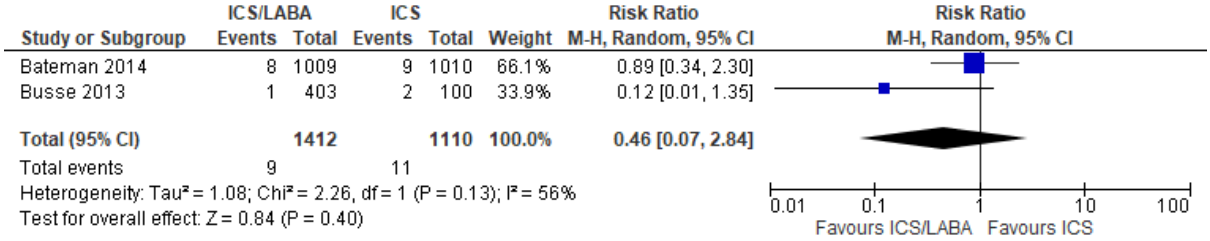


Figure 77: Reliever/rescue medication use (puffs per day, change scores, lower is better)

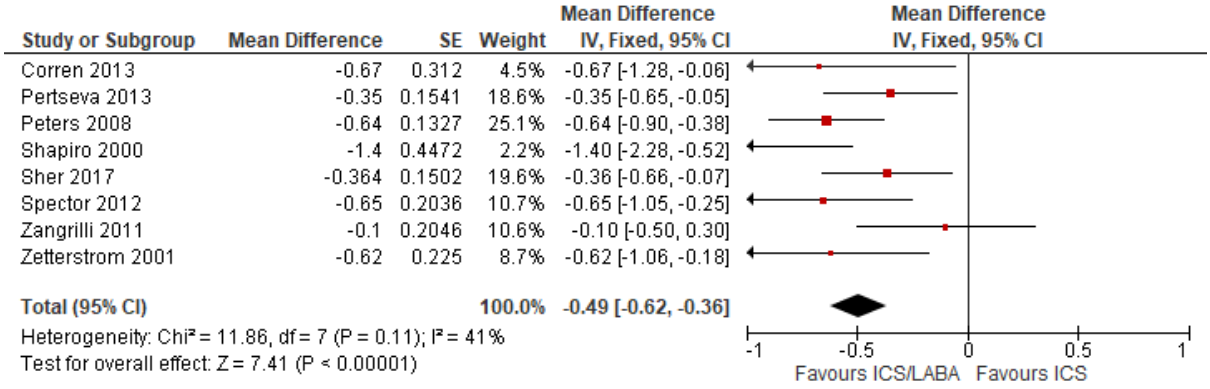


Figure 78: Reliever/rescue medication use (reliever free days or % of days, change scores, higher is better)

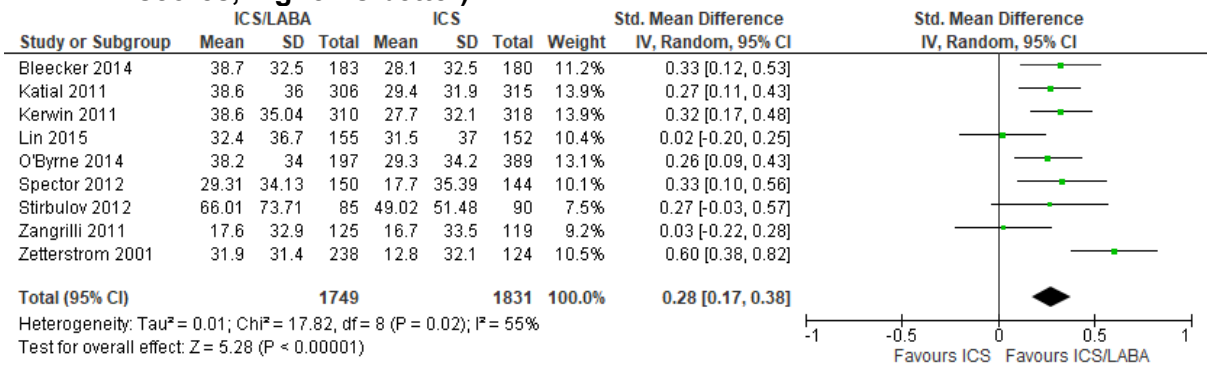


Figure 79: Lung function (FEV_1, litres, mixed values, higher is better)

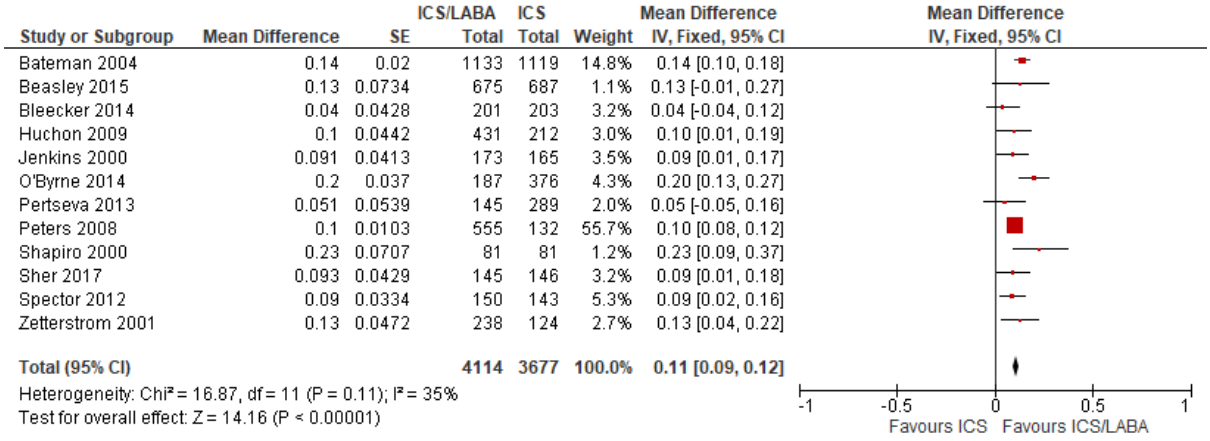


Figure 80: Lung function (FEV_1, % of predicted, mixed values, higher is better)

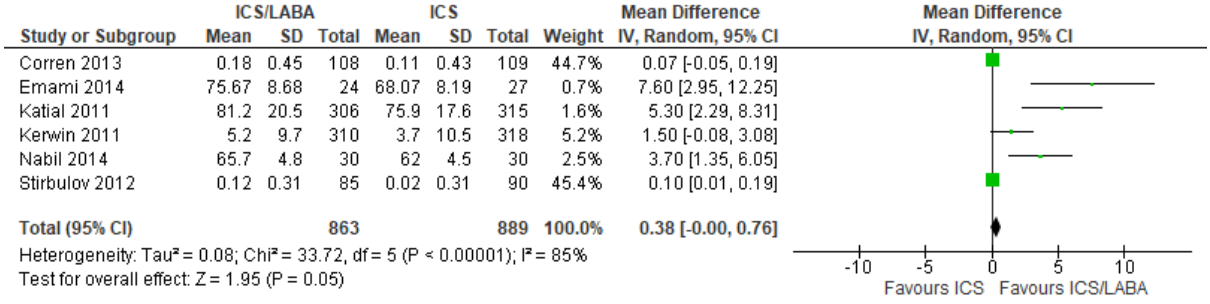


Figure 81: Lung function (PEF, L/min, mixed values, higher is better)

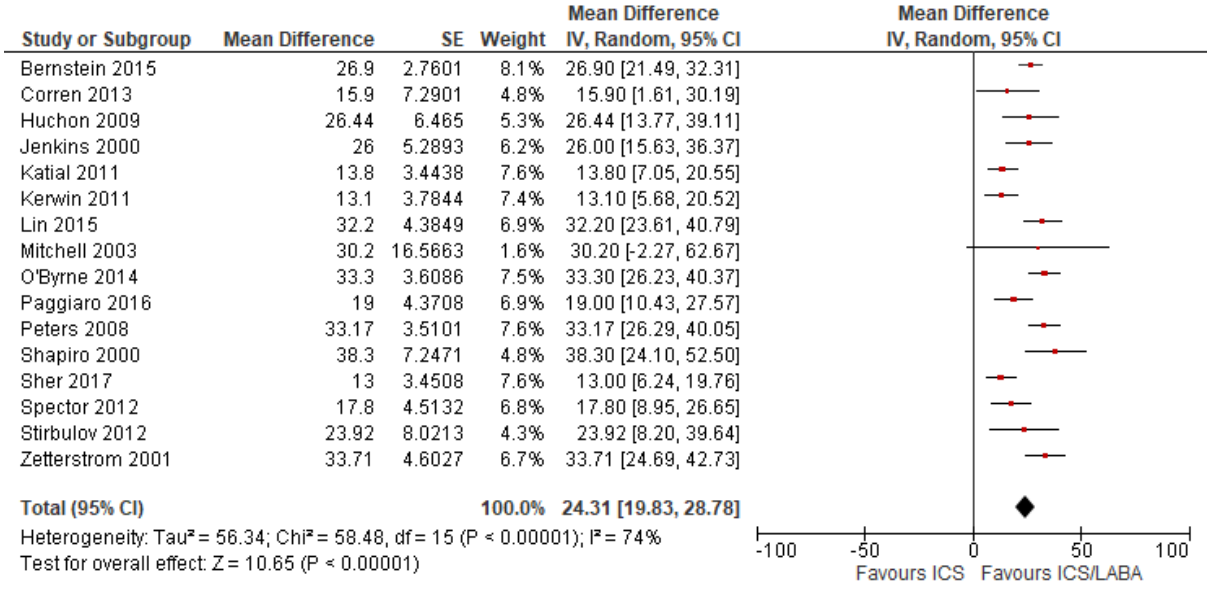


Figure 82: Adverse events (final values, lower is better)

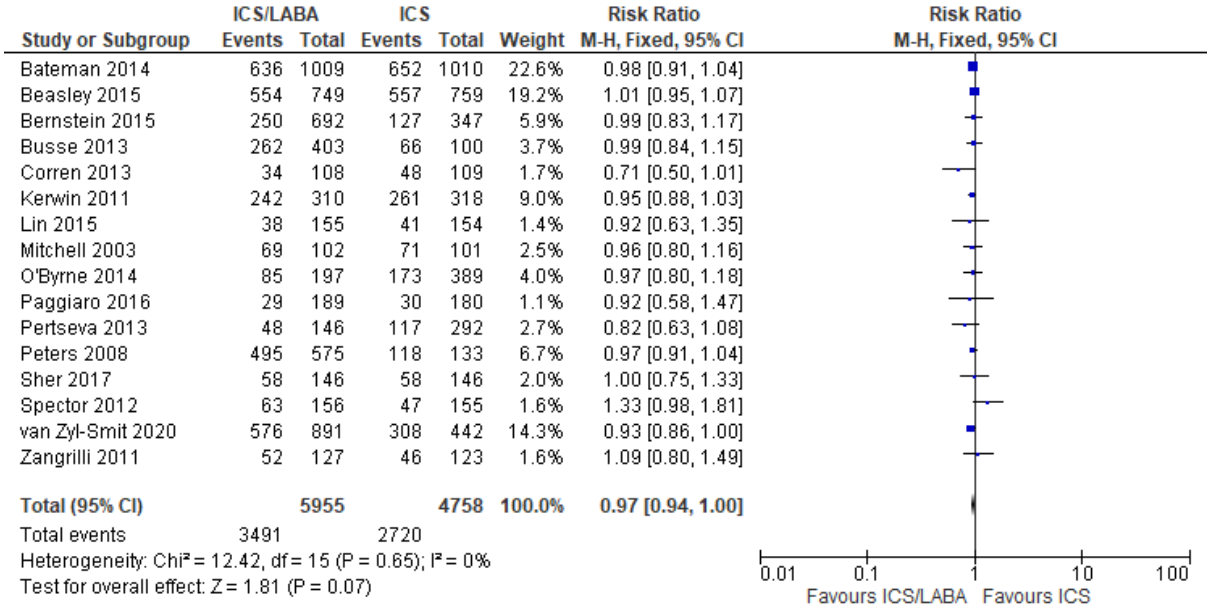


Figure 83: Pneumonia (including respiratory tract infections, final values, lower is better)

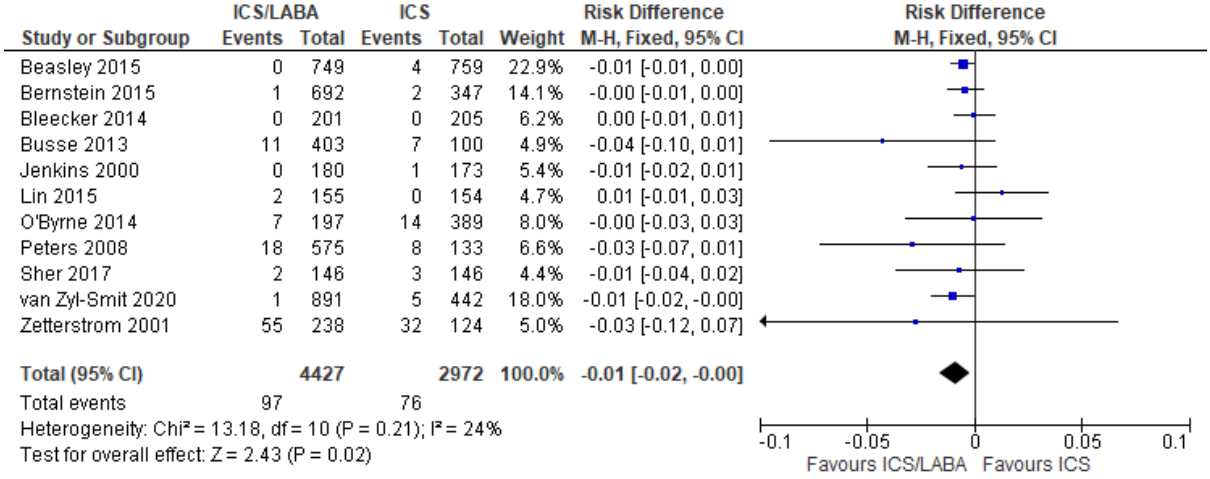


Figure 84: Adrenal insufficiency (cortisol/creatinine ratio, change scores, lower is better)

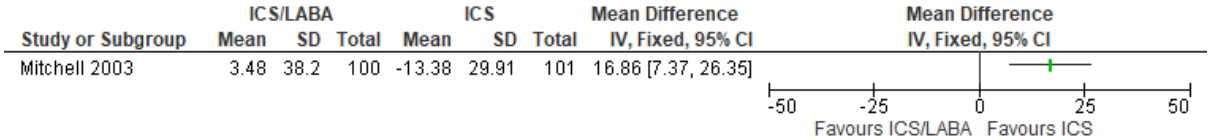


Figure 85: Adrenal insufficiency (serum cortisol, 0-24h AUC, change scores, higher is better)

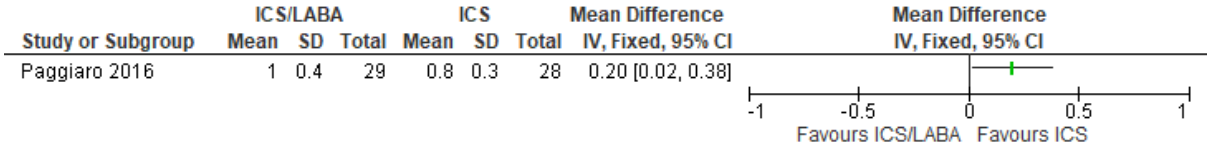
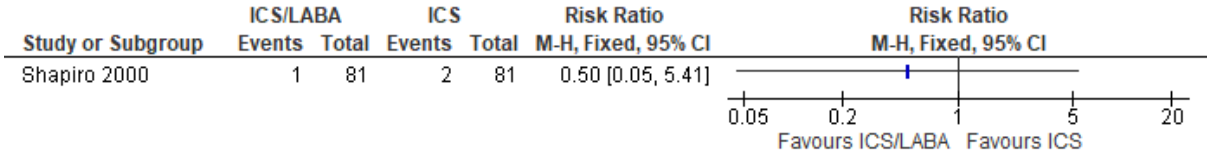


Figure 86: Adrenal insufficiency (morning cortisol <5 mcg/dL, final values, lower is better)



Regular moderate/high dose ICS/LABA with SABA prn vs regular low/moderate dose ICS plus montelukast with SABA prn

Figure 87: Severe asthma exacerbations at 3-5 months (final values, lower is better)

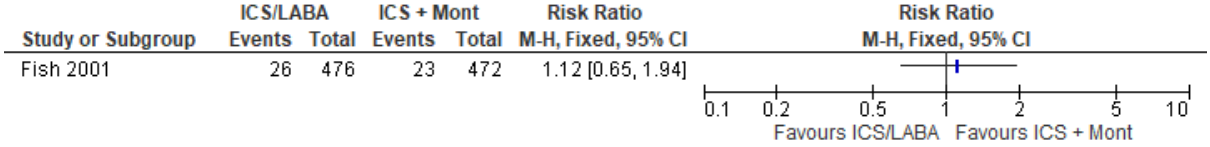


Figure 88: Severe exacerbation rate (rate per person year, final values, lower is better)

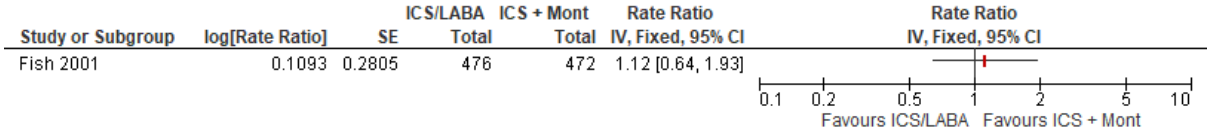


Figure 89: Mortality (final values, lower is better)

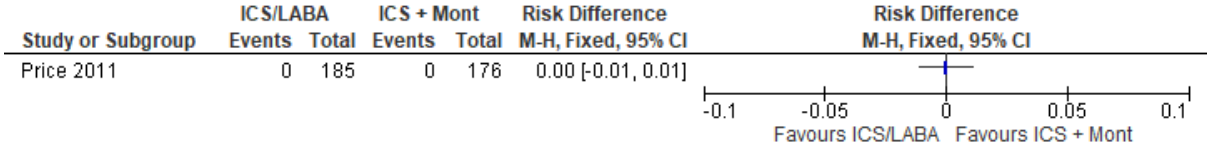


Figure 90: Quality of life (Asthma Quality of Life Questionnaire, scale range 1-7, final values, higher is better)

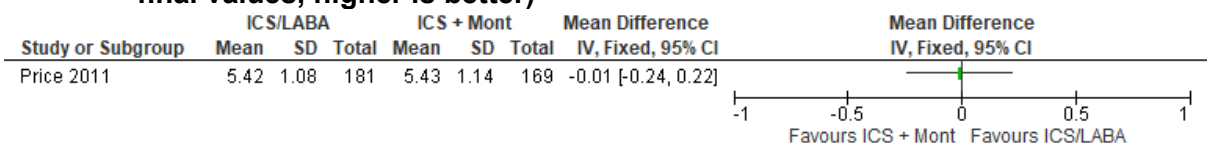


Figure 91: Quality of life (EQ-5D, scale range: 0-1, final values, higher is better)

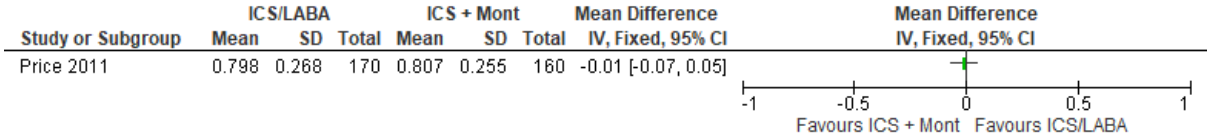


Figure 92: Asthma control (Asthma Control Questionnaire, scale range: 0-6, final values, lower is better)

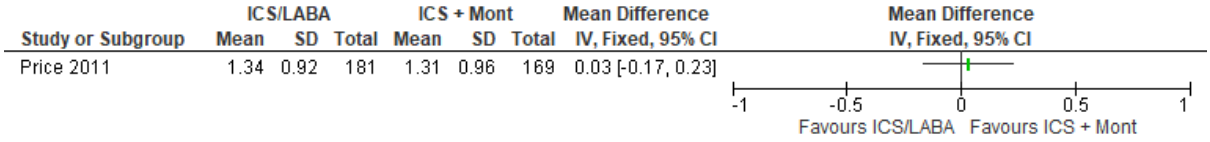


Figure 93: Hospital admissions at ≥6 months (final values, lower is better)

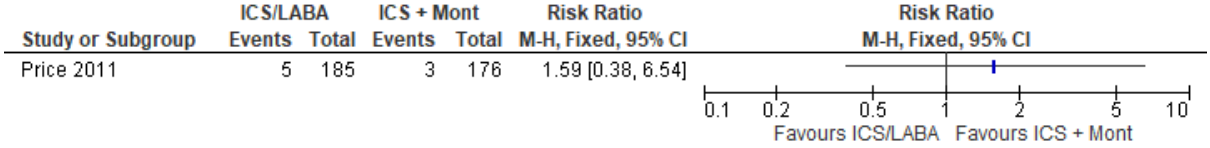


Figure 94: Reliever/rescue medication use (puffs per day, change scores, lower is better)

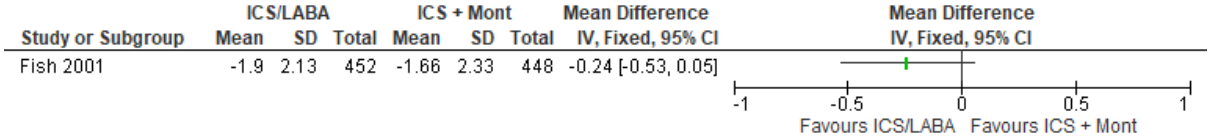


Figure 95: Reliever/rescue medication use (nighttime reliever use, final values, lower is better)

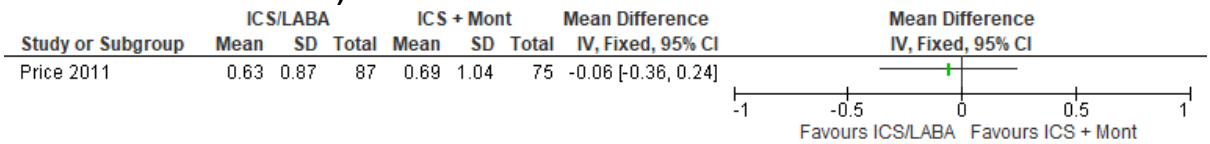


Figure 96: Reliever/rescue medication use (daytime reliever use, final values, lower is better)

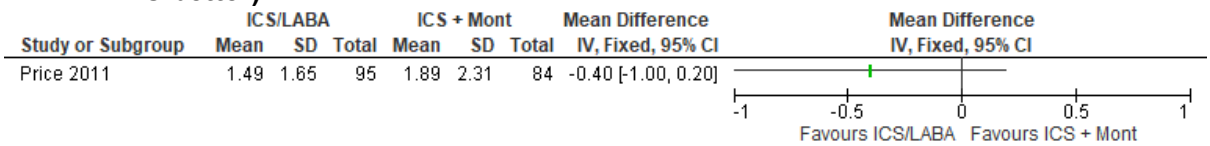


Figure 97: Lung function (PEF, L/min, mixed values, higher is better)

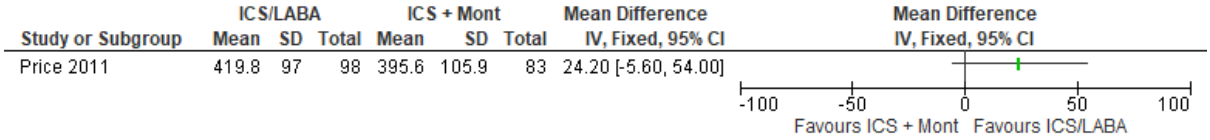
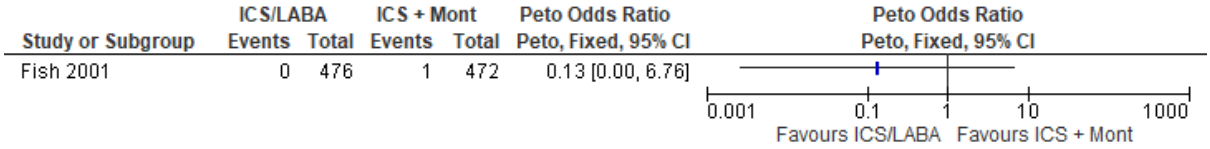


Figure 98: Pneumonia (final values, lower is better)



Regular low/moderate dose ICS/LABA plus montelukast with SABA prn vs regular low/moderate dose ICS/LABA plus LAMA with SABA prn

Figure 99: Severe asthma exacerbations at ≥6 months (final values, lower is better)

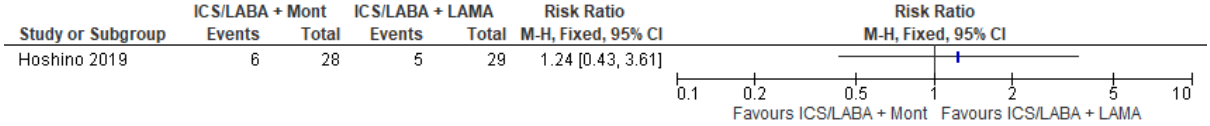


Figure 100: Quality of life (Asthma Quality of Life Questionnaire, symptom domain, scale range: 0-7, change scores, higher is better)

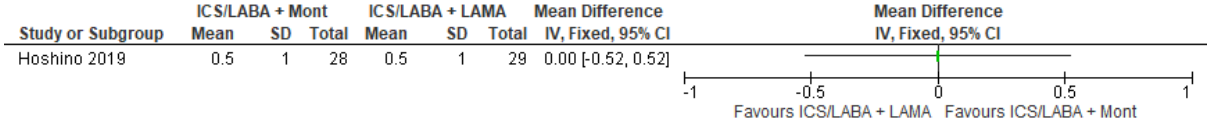


Figure 101: Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)

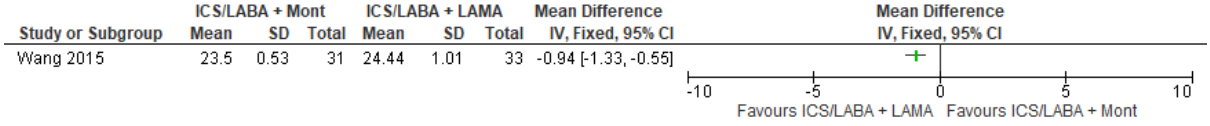


Figure 102: Lung function (FEV_1, % of predicted, change scores, higher is better)

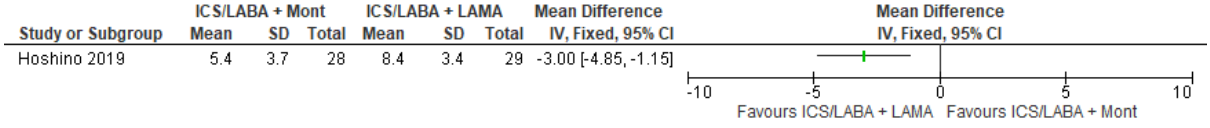
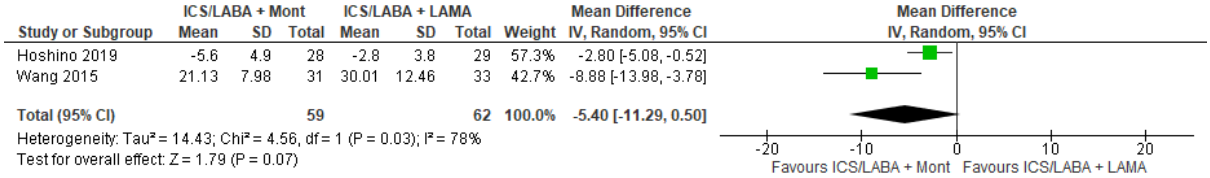


Figure 103: Inflammatory markers (FeNO, ppb, mixed values, lower is better)



Regular moderate/high dose ICS/LABA with SABA prn vs regular low/moderate dose ICS plus LAMA with SABA prn

Figure 104: Severe asthma exacerbations at 3-5 months (final values, lower is better)

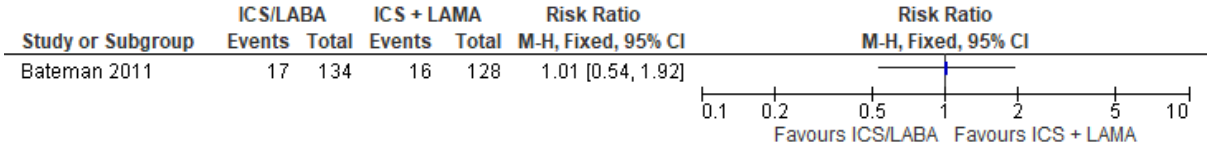


Figure 105: Severe asthma exacerbations at ≥6 months (final values, lower is better)

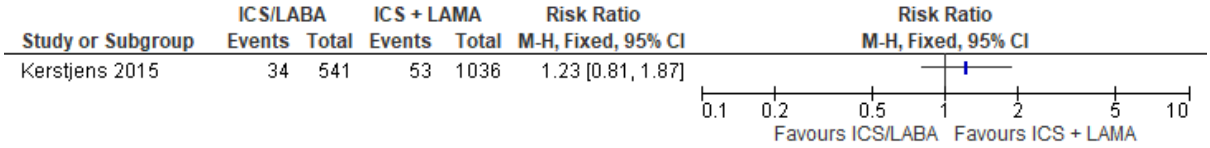


Figure 106: Mortality (final values, lower is better)

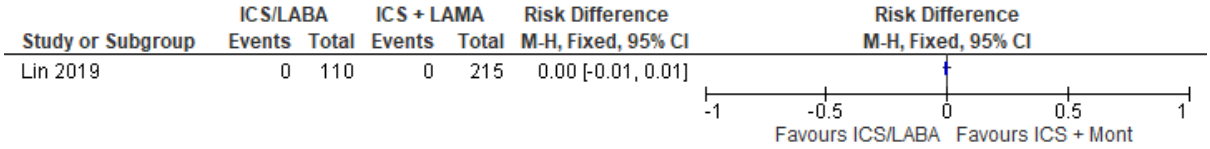


Figure 107: Quality of life (Mini Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)

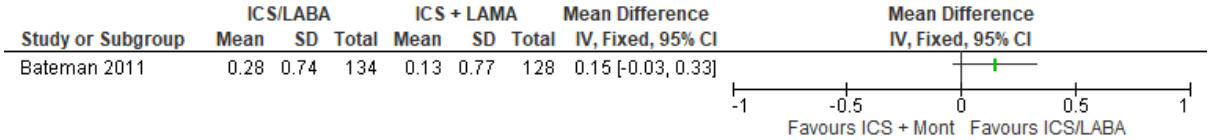


Figure 108: Hospital admissions at 3-5 months (final values, lower is better)

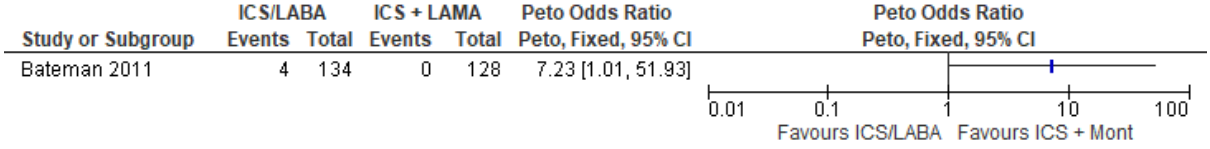


Figure 109: Hospital admissions at ≥6 months (final values, lower is better)

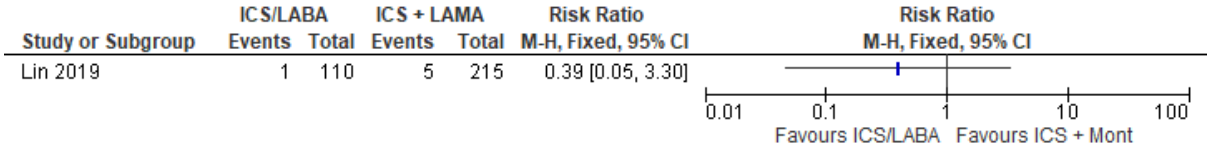


Figure 110: Reliever/rescue medication use (puffs per day, change scores, lower is better)

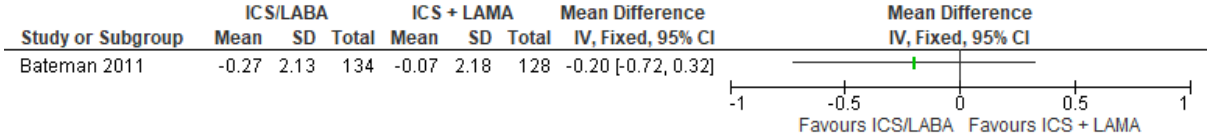


Figure 111: Lung function (FEV_1, litres, change scores, higher is better)

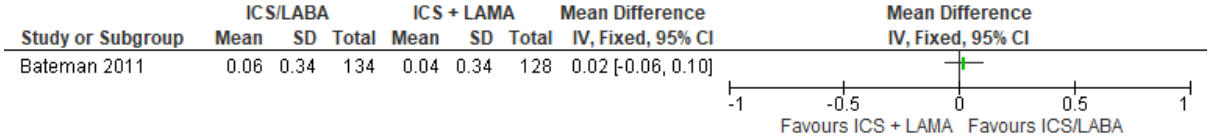


Figure 112: Lung function (PEF, L/min, change scores, higher is better)

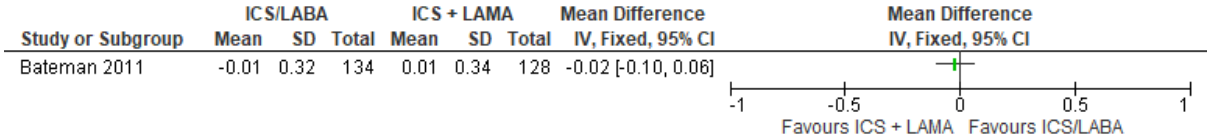


Figure 113: Adverse events (final values, lower is better)

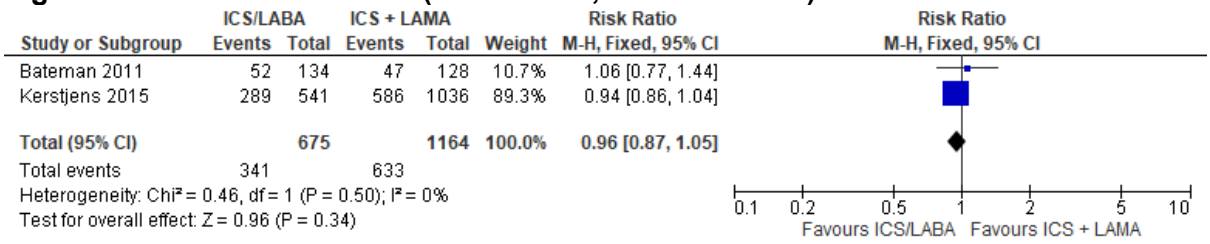
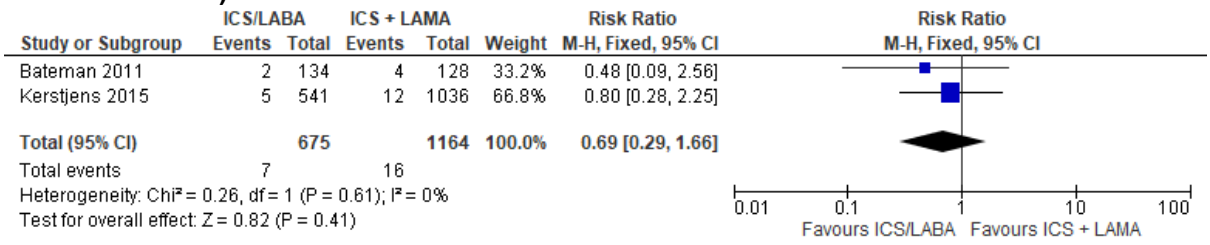


Figure 114: Pneumonia (including respiratory tract infections, final values, lower is better)



Regular moderate/high dose ICS with SABA prn vs regular low/moderate dose ICS plus montelukast with SABA prn

Figure 115: Severe asthma exacerbations at 3-5 months (final values, lower is better)

Figure 116: Severe exacerbation rate (rate per person year, final values, lower is better)

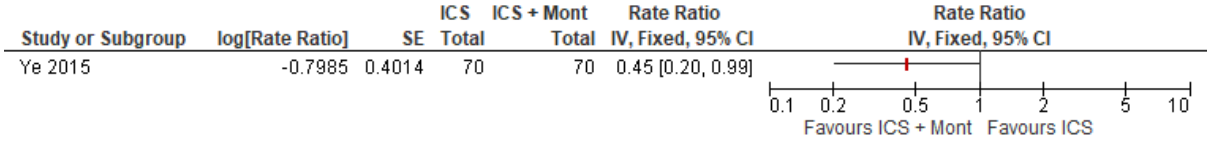


Figure 117: Quality of life (Asthma quality of life questionnaire, scale range: 1-7, final values, higher is better)

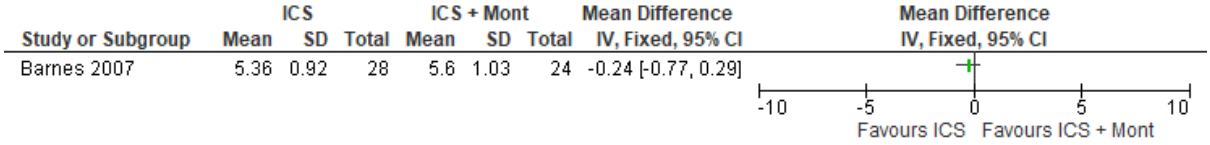


Figure 118: Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)

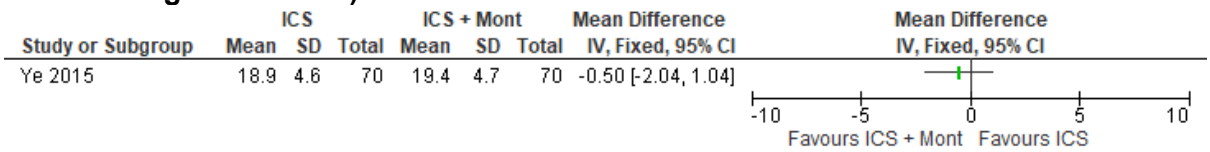


Figure 119: Reliever/rescue medication use (puffs per day, change scores, lower is better)

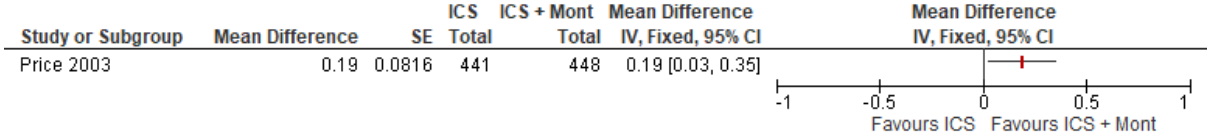


Figure 120: Lung function (FEV_1, % of predicted, change scores, higher is better)

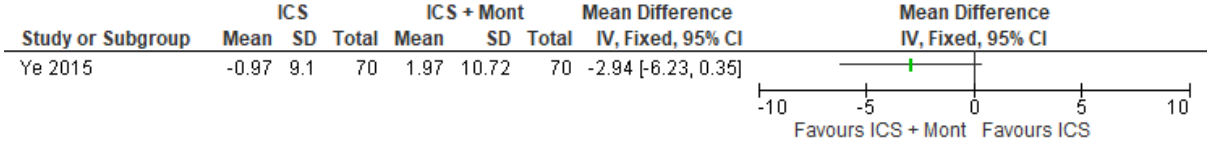


Figure 121: Lung function (PEF, L/minute, change scores, higher is better)

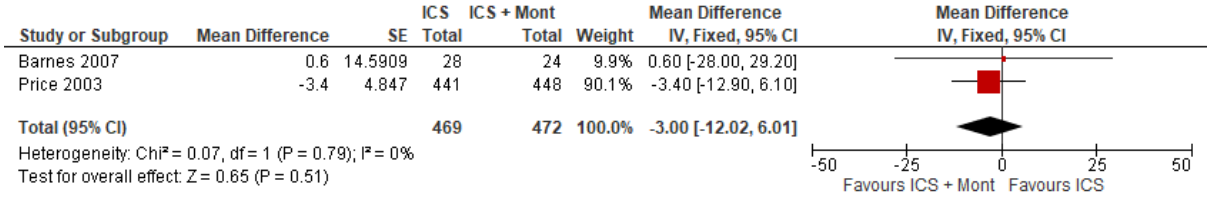


Figure 122: Adverse events (final values, lower is better)

E.3 Children aged 5-11 years

Regular paediatric moderate/high dose ICS with SABA prn vs regular paediatric moderate/high dose ICS/LABA with SABA prn

Figure 123: Severe asthma exacerbations at 3-5 months (final values, lower is better)

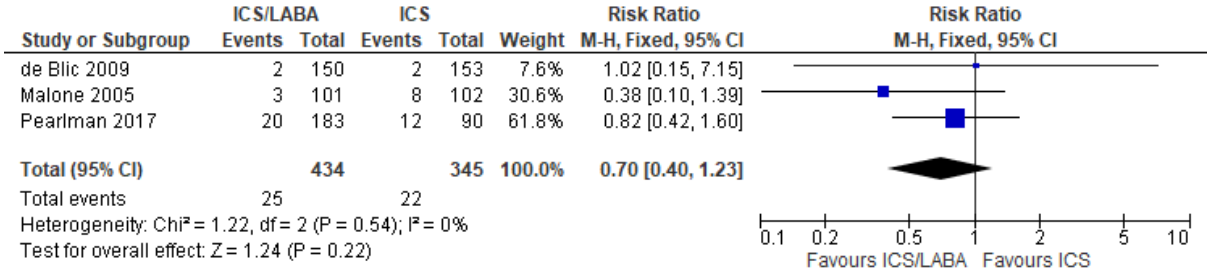


Figure 124: Severe asthma exacerbations at ≥6 months (final values, lower is better)

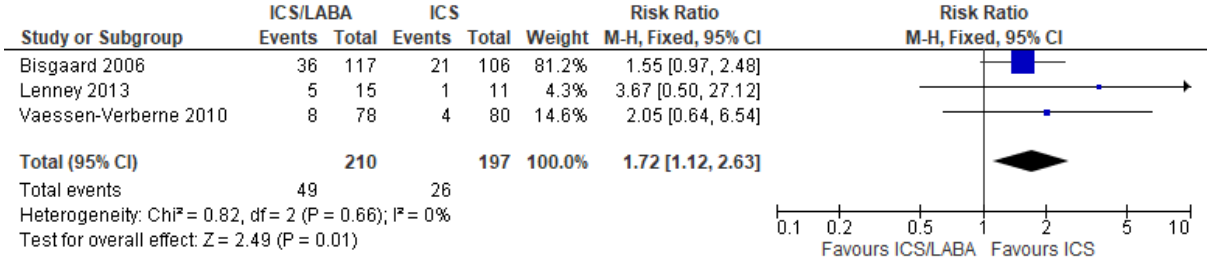


Figure 125: Severe exacerbation rate (events per person year, lower is better)

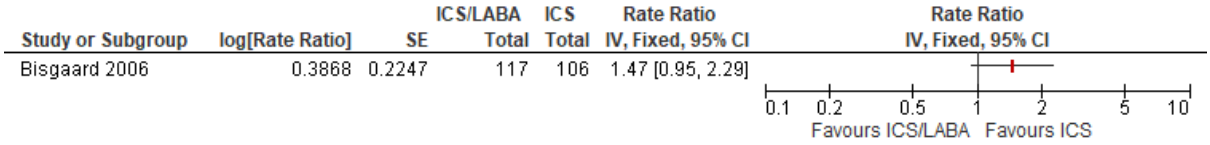


Figure 126: Mortality (final values, lower is better)

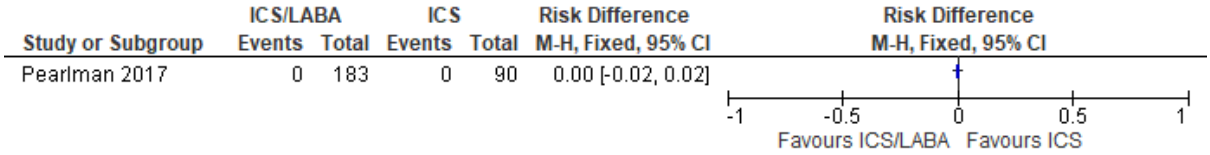


Figure 127: Quality of life (PAQLQ, scale range: 1-7, change scores, lower is better)

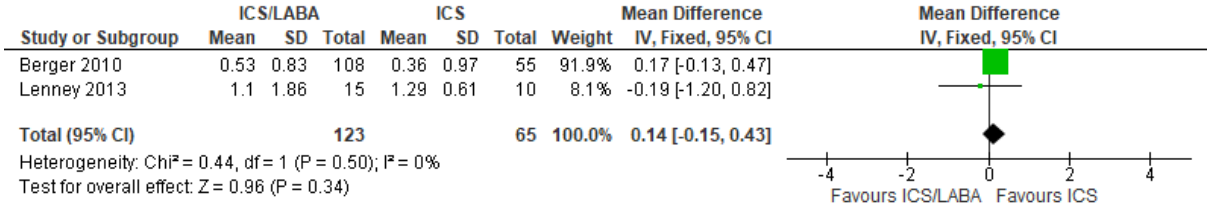


Figure 128: Hospital admissions (final values, lower is better)

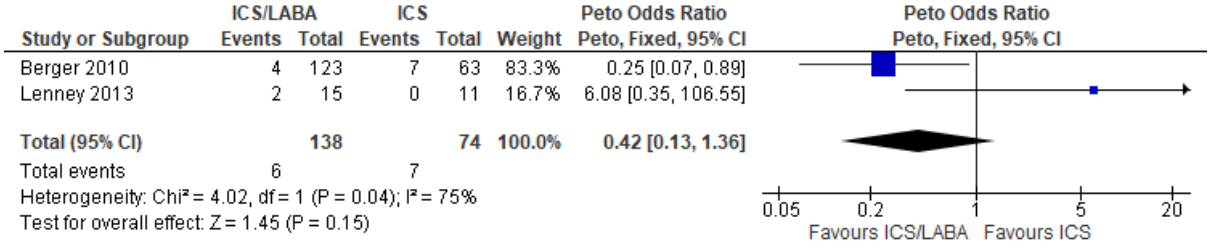


Figure 129: Reliever/rescue medication use (puffs per day, mixed values, lower is better)

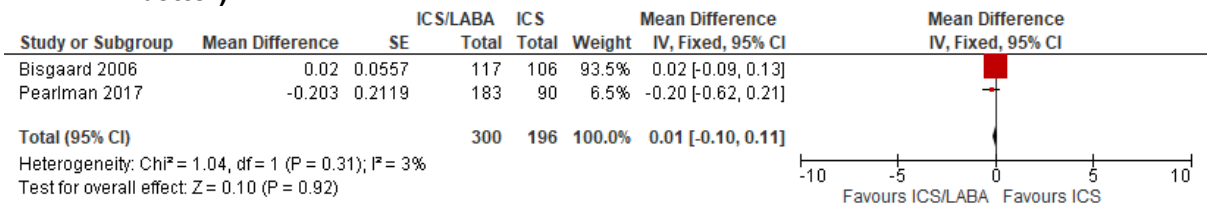


Figure 130: Reliever/rescue medication use (reliever-free days, % of days, final values, higher is better)

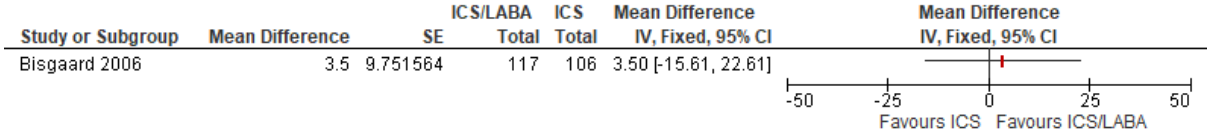


Figure 131: Lung function (PEF, % of predicted, final values, higher is better)

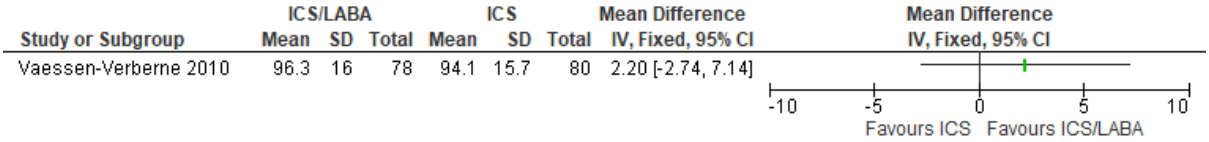


Figure 132: Lung function (PEF, L/min, mixed values, higher is better)

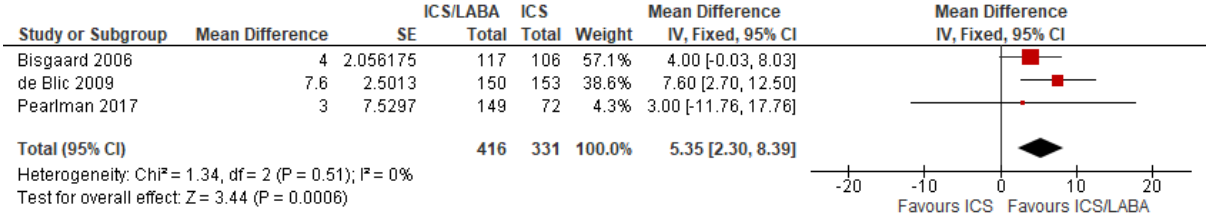


Figure 133: Lung function (FEV_1, % of predicted, mixed values, higher is better)

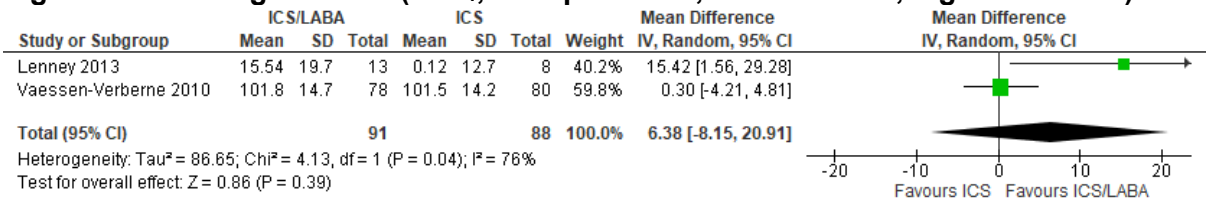


Figure 134: Adverse events (final values, lower is better)

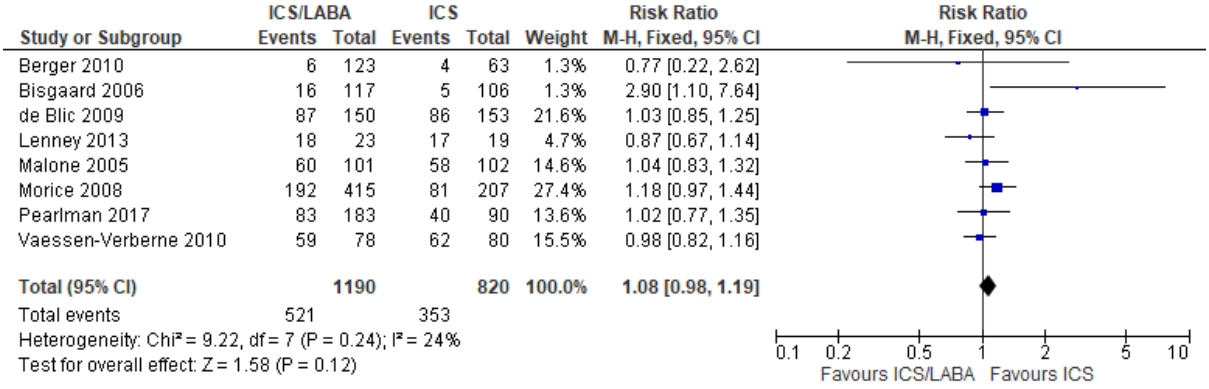


Figure 135: Pneumonia (including lower respiratory tract infections, final values, lower is better)

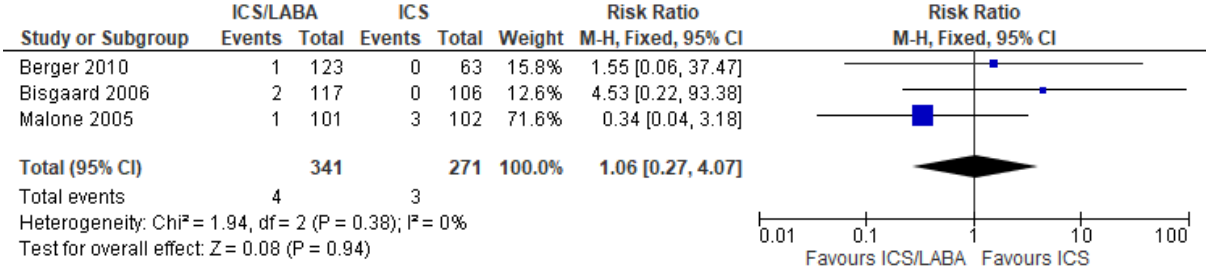
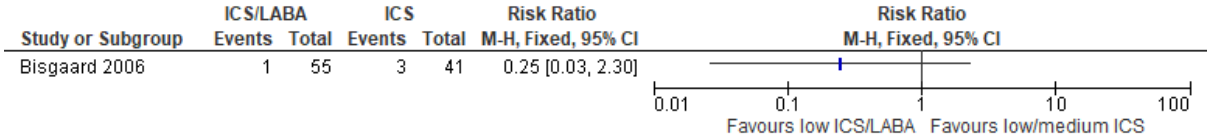


Figure 136: Adrenal insufficiency (number of participants with morning cortisol <400 nmol/L, final values, lower is better)



ICS/formoterol maintenance and reliever therapy (MART) vs regular paediatric moderate/high dose ICS/LABA with SABA prn

Figure 137: Severe asthma exacerbations at ≥6 months (final values, lower is better)

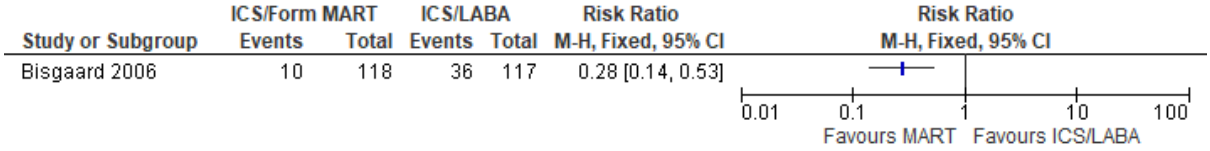


Figure 138: Severe exacerbation rate (events per person year, lower is better)

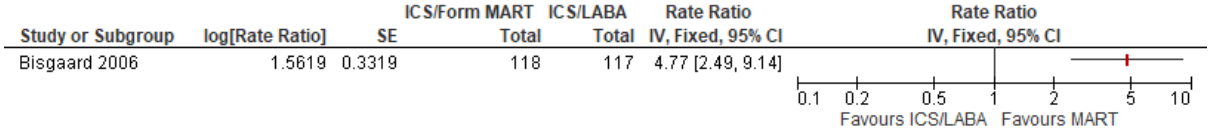


Figure 139: Reliever/rescue medication use (puffs per day, final values, lower is better

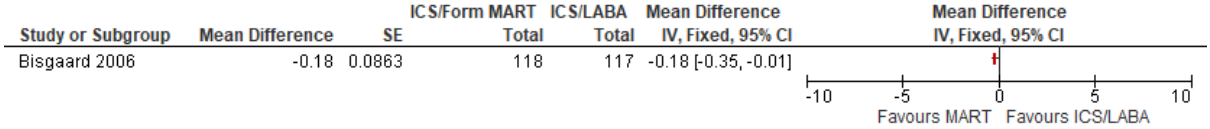


Figure 140: Reliever/rescue medication use (reliever-free days, % of days, final values, higher is better)

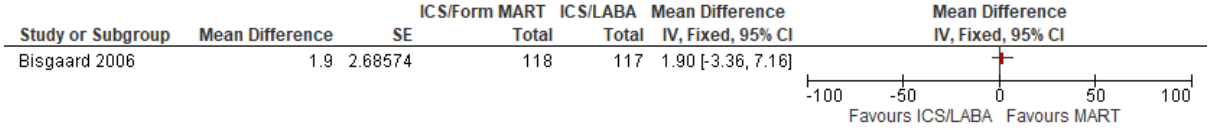


Figure 141: Lung function (PEF, L/min, final values, higher is better)

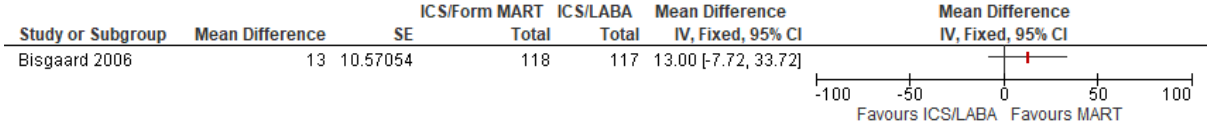


Figure 143: Adverse events (final values, lower is better)

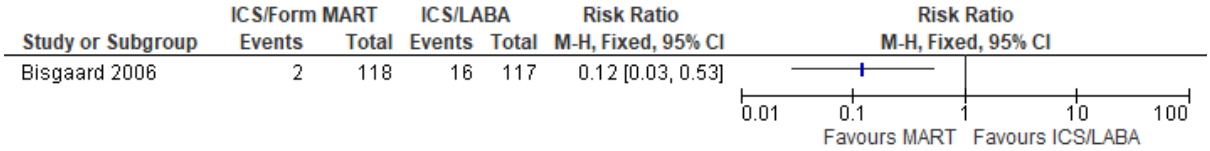


Figure 144: Pneumonia (final values, lower is better)

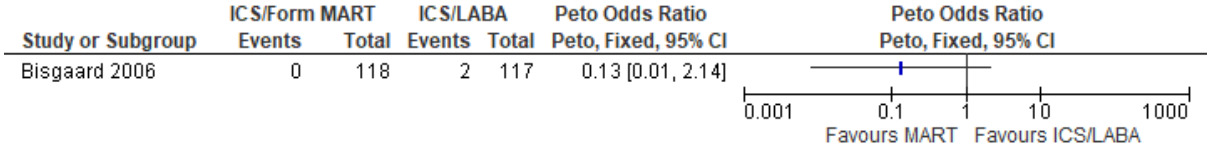
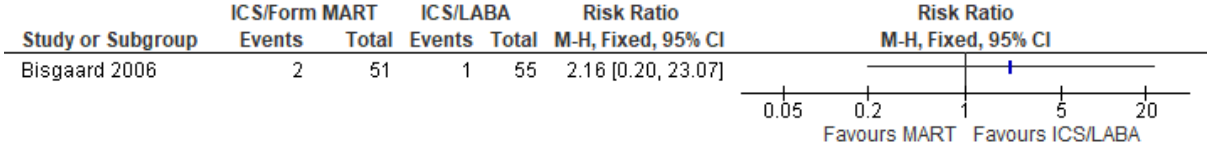


Figure 145: Adrenal insufficiency (number of participants with morning cortisol <400 nmol/L, final values, lower is better)



ICS/formoterol maintenance and reliever therapy (MART) vs regular paediatric moderate/high dose ICS with SABA prn

Figure 146: Severe asthma exacerbations at ≥6 months (final values, lower is better)

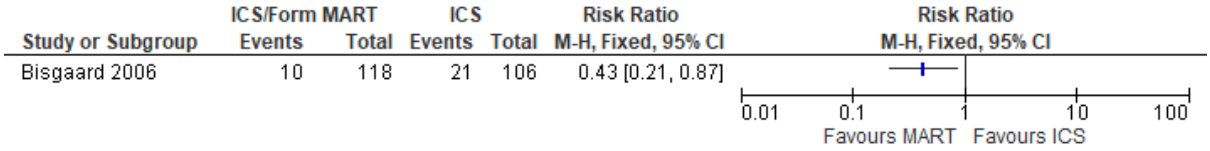


Figure 147: Severe exacerbation rate (events per person year, lower is better)

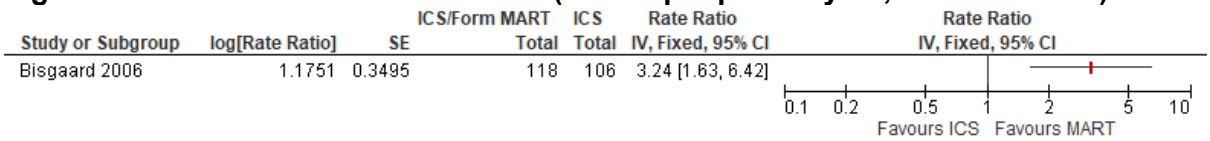


Figure 148: Reliever/rescue medication use (puffs per day, final values, lower is better)

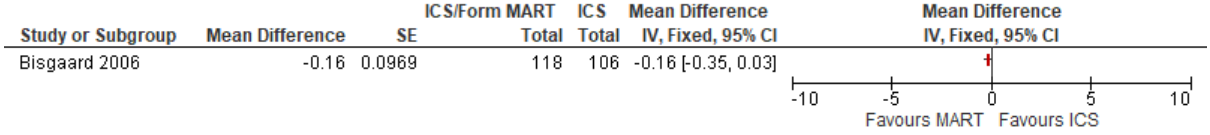


Figure 149: Reliever/rescue medication use (reliever-free days, % of days, final values, higher is better)

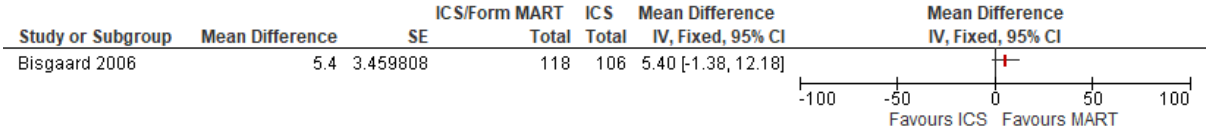


Figure 150: Lung function (PEF, L/min, final values, higher is better)

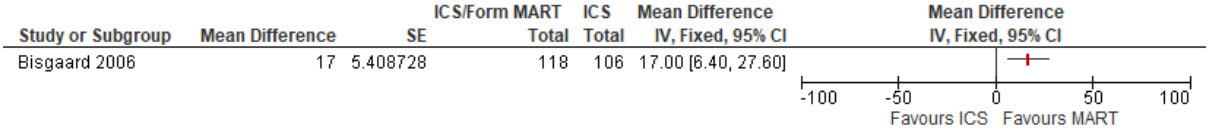


Figure 151: Adverse events (final values, lower is better)

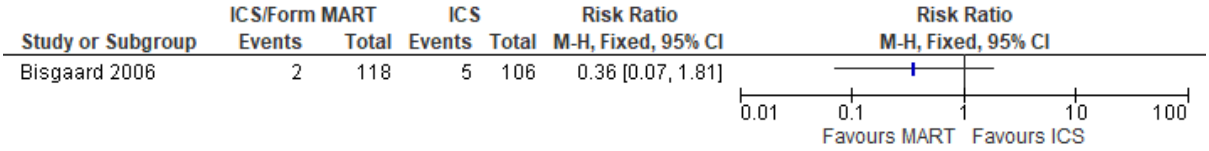


Figure 652: Pneumonia (final values, lower is better)

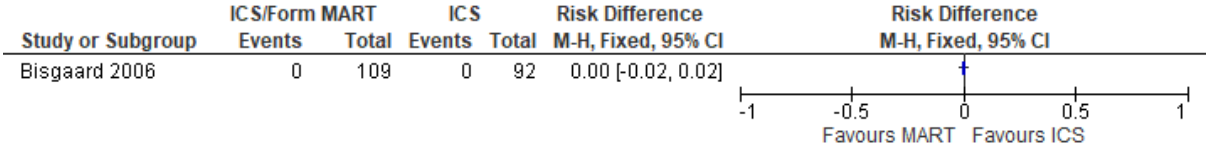
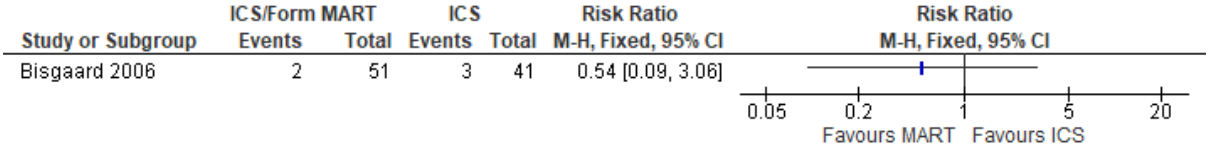


Figure 153: Adrenal insufficiency (number of participants with morning cortisol <400 nmol/L, final values, lower is better)



ICS Regular paediatric moderate/high dose ICS with SABA prn vs regular paediatric moderate dose ICS plus montelukast with SABA prn

Figure 154: Severe asthma exacerbations at ≥6 months (final values, lower is better)

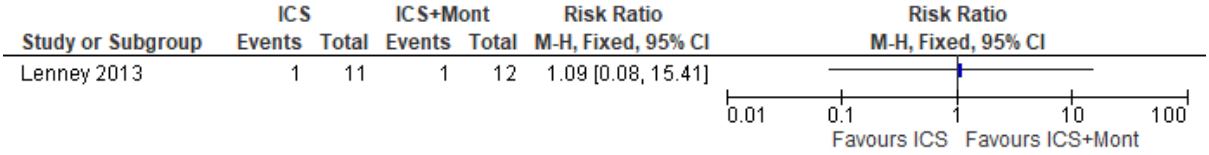


Figure 155: Quality of life (Paediatric Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)

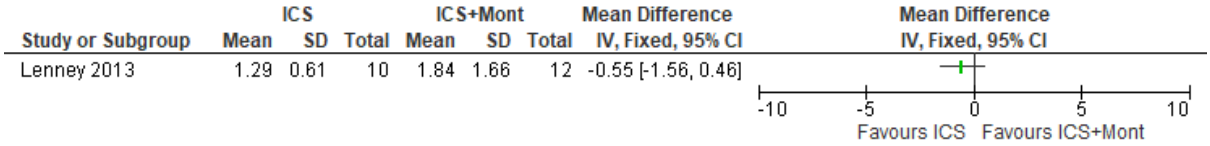


Figure 156: Hospital admissions (final values, lower is better)

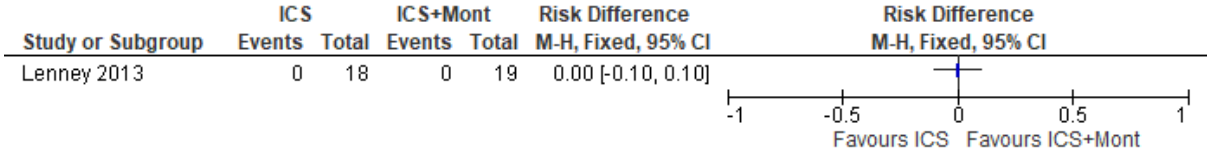


Figure 157: Lung function (FEV_1, % of predicted, change scores, higher is better)

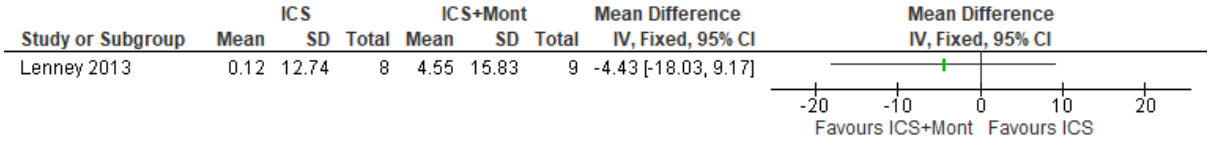
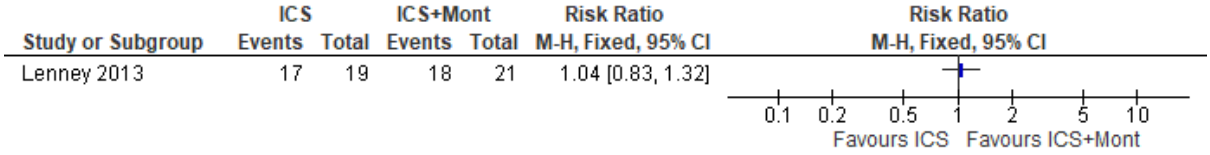


Figure 158: Adverse events (final values, lower is better)



Regular paediatric moderate/high dose ICS/LABA with SABA prn vs regular paediatric moderate dose ICS plus montelukast with SABA prn

Figure 159: Severe asthma exacerbations at ≥6 months (final values, lower is better)

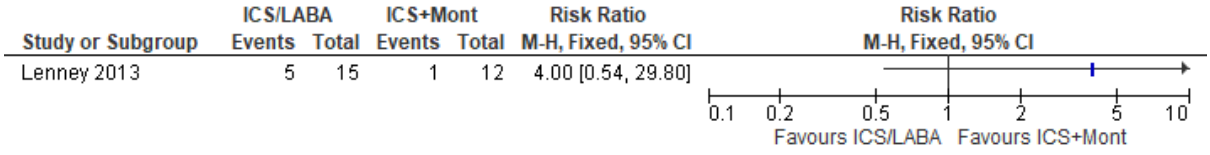


Figure 160: Quality of life (Paediatric Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)

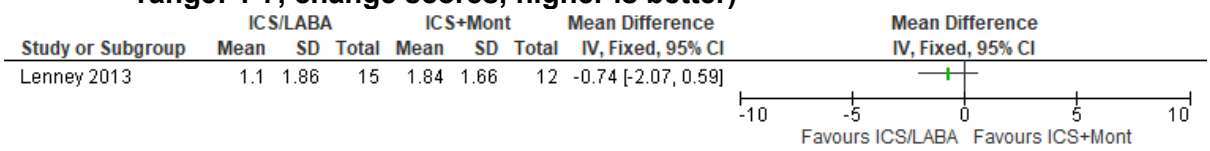


Figure 161: Hospital admissions (final values, lower is better)

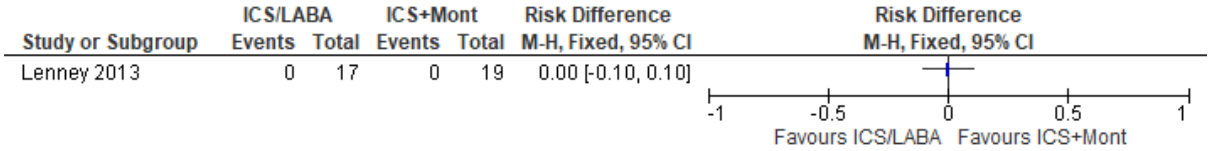


Figure 162: Lung function (FEV_1, % of predicted, change scores, higher is better)

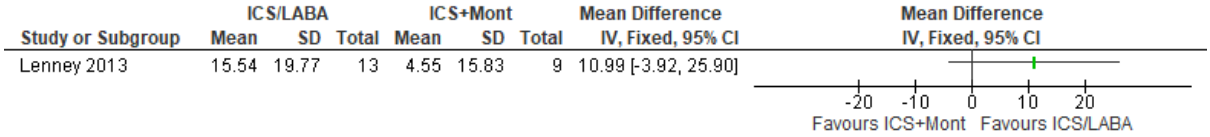
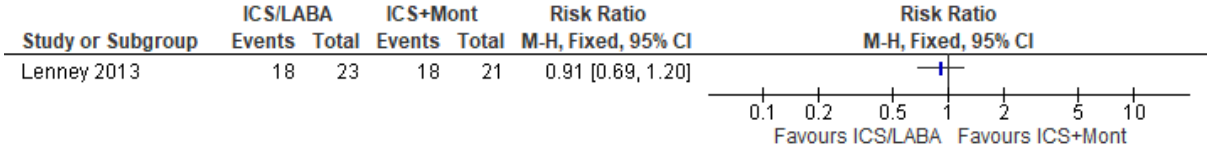


Figure 163: Adverse events (final values, lower is better)



E.4 Children under 5 years

Regular ICS vs as-needed ICS/SABA

Figure 164: Severe asthma exacerbations at 3-5 months (final values, lower is better)

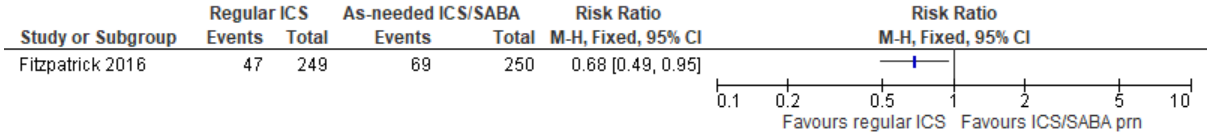


Figure 165: Hospital admissions at 3-5 months (final values, lower is better)

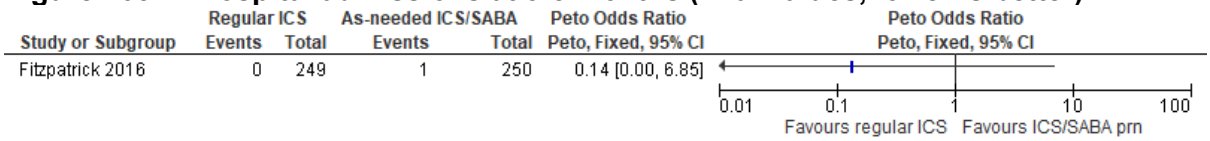
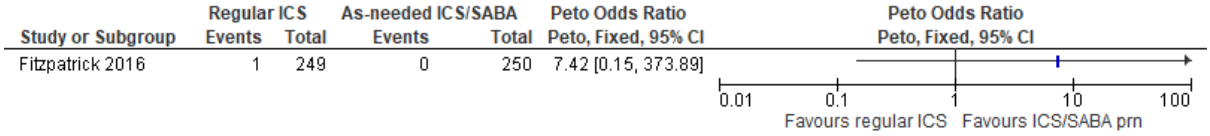


Figure 166: Pneumonia (final values, lower is better)



Regular ICS vs regular montelukast

Figure 167: Severe asthma exacerbations at 3-5 months (final values, lower is better)

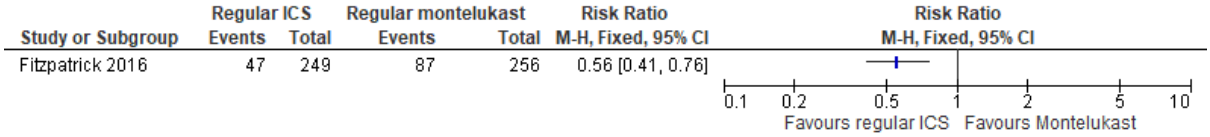


Figure 168: Severe asthma exacerbations at ≥6 months (final values, lower is better)

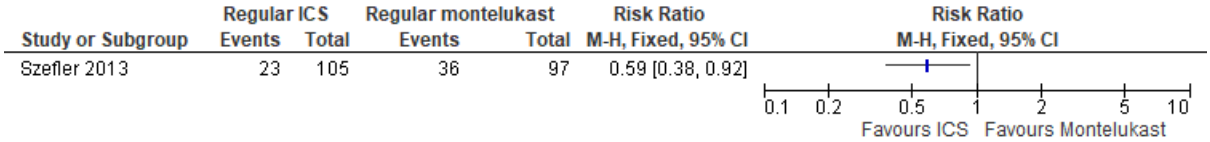


Figure 169: Mortality (final values, lower is better)

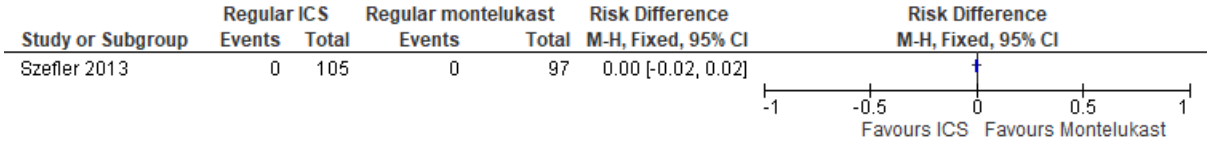


Figure 170: Hospital admissions at 3-5 months (final values, lower is better)

Figure 171: Reliever/rescue medication use (puffs per day, change scores, lower is better)

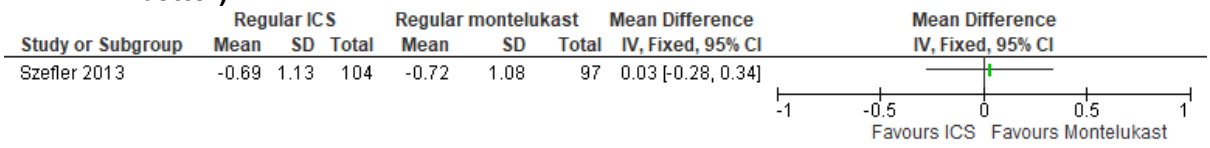


Figure 172: Lung function (PEF, L/minute, change scores, higher is better)

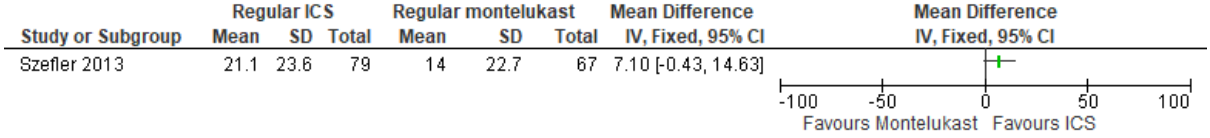


Figure 173: Adverse events (final values, lower is better)

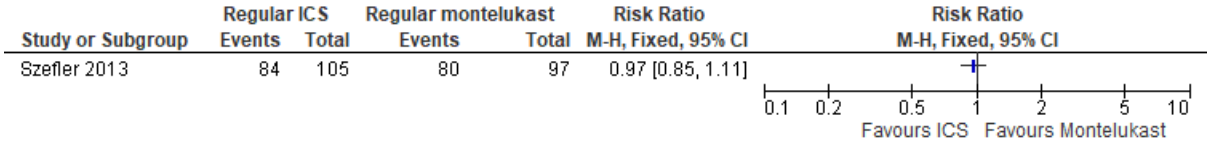
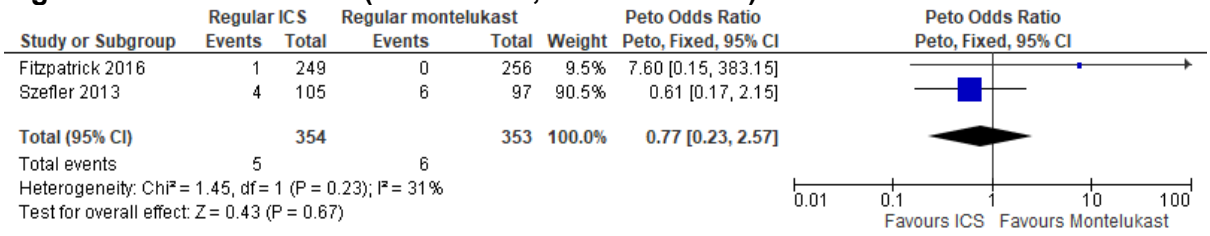


Figure 174: Pneumonia (final values, lower is better)



As-needed ICS/SABA vs regular montelukast

Figure 175: Severe asthma exacerbations at 3-5 months (final values, lower is better)

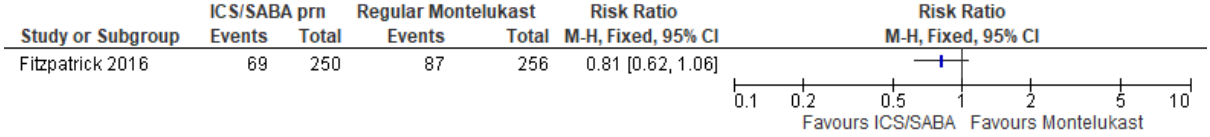


Figure 176: Hospital admissions at 3-5 months (final values, lower is better)

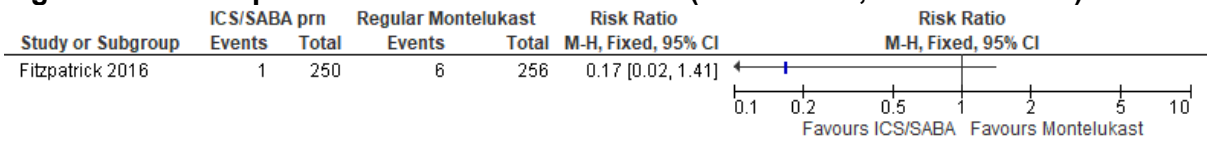
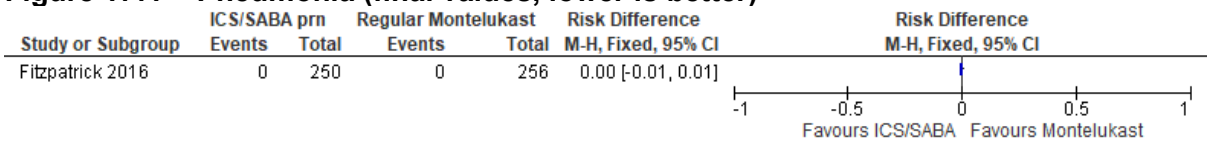


Figure 177: Pneumonia (final values, lower is better)



Appendix F – GRADE tables

First add-on treatment in adults and young people aged ≥12 years with uncontrolled asthma

Table 15: Clinical evidence profile: regular low dose ICS/LABA with SABA prn vs regular low dose ICS with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular ICS/LABA	Regular ICS	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at 3-5 months (final values, lower is better)												
5	randomised trials	serious[a]	serious[b]	not serious	very serious[c]	none	26/701 (3.7%)	32/716 (4.5%)	**RR 0.82** (0.46 to 1.45)	**8 fewer per 1,000** (from 24 fewer to 20 more)	⨁◯◯◯ Very low	CRITICAL
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
2	randomised trials	very serious[d]	not serious	not serious	very serious[e]	none	47/317 (14.8%)	54/308 (17.5%)	not estimable	**20 more per 1,000** (from 30 fewer to 80 more)	⨁◯◯◯ Very low	CRITICAL
Severe exacerbation rate (per patient year, lower is better)												
3	randomised trials	very serious[d]	not serious	not serious	serious[f]	none	750/641	970/653	**Rate ratio 0.77** (0.57 to 1.05)	-	⨁◯◯◯ Very low	CRITICAL
Mortality (final values, lower is better)												
4	randomised trials	very serious[g]	not serious	not serious	very serious[e]	none	0/885 (0.0%)	1/903 (0.1%)	not estimable	**0 fewer per 1,000** (from 0 fewer to 10 more)	⨁◯◯◯ Very low	CRITICAL
Asthma control (Asthma Control Questionnaire-7, scale range 0-6, change scores, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular ICS/LABA	Regular ICS	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[g]	not serious	not serious	not serious	none	387	384	-	MD **0.22 lower** (0.33 lower to 0.1 lower)	⨁⨁◯◯ Low	CRITICAL
Hospital admissions at 3-5 months (final values, lower is better)												
1	randomised trials	very serious[g]	not serious	not serious	very serious[c]	none	0/398 (0.0%)	1/404 (0.2%)	**OR 0.14** (0.00 to 6.92)	**2 fewer per 1,000** (from -- to 14 more)	⨁◯◯◯ Very low	CRITICAL
Hospital admissions at ≥6 months (final values, lower is better)												
2	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	5/492 (1.0%)	6/502 (1.2%)	**RR 0.85** (0.26 to 2.77)	**2 fewer per 1,000** (from 9 fewer to 21 more)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (puffs per day, change scores, lower is better)												
5	randomised trials	serious[a]	not serious	not serious	not serious	none	790	805	-	MD **0.19 lower** (0.28 lower to 0.11 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (SABA-free days, %, mixed values, higher is better)												
6	randomised trials	very serious[h]	not serious	not serious	not serious	none	1069	868	-	MD **8.73 higher** (5.85 higher to 11.61 higher)	⨁⨁◯◯ Low	CRITICAL
Lung function (FEV1, litres, change scores, higher is better)												
7	randomised trials	very serious[h]	serious[b]	not serious	not serious	none	1276	1289	-	MD **0.13 higher** (0.05 higher to 0.21 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular ICS/LABA	Regular ICS	Relative (95% CI)	Absolute (95% CI)		
Lung function (PEF, L/minute, change scores, higher is better)												
5	randomised trials	very serious[h]	not serious	not serious	not serious	none	1217	1014	-	MD **22.5 higher** (18.91 higher to 26.08 higher)	⨁⨁◯◯ Low	CRITICAL
Lung function (PEF, % of predicted, change scores, higher is better)												
1	randomised trials	serious[i]	not serious	not serious	serious[i]	none	88	89	-	MD **6.8 higher** (3.4 higher to 10.2 higher)	⨁⨁◯◯ Low	CRITICAL
Pneumonia (including respiratory tract infections, final values, lower is better)												
3	randomised trials	serious[a]	not serious	serious[k]	very serious[c]	none	92/1388 (6.6%)	69/1203 (5.7%)	**OR 0.97** (0.69 to 1.37)	**2 fewer per 1,000** (from 17 fewer to 20 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events (final values, lower is better)												
9	randomised trials	very serious[h]	not serious	not serious	not serious	none	556/1694 (32.8%)	565/1498 (37.7%)	**RR 0.93** (0.85 to 1.01)	**26 fewer per 1,000** (from 57 fewer to 4 more)	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by one increment due to concerns arising from the method of randomisation (method not reported) in the majority of the evidence

b. Downgraded by one increment due to heterogeneity that was unexplained by random effects model

c. Downgraded by two increments due to the 95%CI overlapping both the upper and lower MID (0.8-1.25)

d. Downgraded by two increments due to concerns arising from the randomisation process (method not reported) and missing outcome data in the majority of the evidence

e. Downgraded by two increments due to inadequate sample size (power <80%)

f. Downgraded by one increment due to the 95%CI overlapping the lower MID (0.8-1.25)

g. Downgraded by two increments due to concerns arising from the method of randomisation (method not reported) and deviations from the intended interventions (adherence not reported) in the majority of the evidence

h. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended interventions (adherence not reported) and/or missing outcome data in the majority of the evidence

i. Downgraded by one increment due to concerns arising from missing outcome data

j. Downgraded by one increment due to the 95%CI overlapping one MID

k. Downgraded by one increment due to the majority of the evidence being for an outcome that is indirectly relevant to that listed in this review protocol

Table 8: Clinical evidence profile: low dose ICS/formoterol MART vs regular low dose ICS with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA MART	Regular ICS with SABA as-needed	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	38/626 (6.1%)	72/613 (11.7%)	**RR 0.52** (0.35 to 0.75)	**56 fewer per 1,000** (from 76 fewer to 29 fewer)	⨁⨁◯◯ Low	CRITICAL
Severe exacerbation rate (per patient year, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	14/355	57/342	**Rate ratio 0.24** (0.20 to 0.27)	-	⨁⨁⨁◯ Moderate	CRITICAL
Hospital admissions (final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	1/355 (0.3%)	10/342 (2.9%)	**RR 0.10** (0.01 to 0.75)	**26 fewer per 1,000** (from 29 fewer to 7 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (puffs per day, final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	355	342	-	MD **0.34 lower** (0.51 lower to 0.17 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (SABA-free days, %, final values, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA MART	Regular ICS with SABA as-needed	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	not serious	none	355	342	-	MD **8.1 higher** (2.5 higher to 12.7 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (FEV1, litres, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	626	613	-	MD **0.1 higher** (0.07 higher to 0.13 higher)	⨁⨁◯◯ Low	CRITICAL
Lung function (PEF, L/minute, final values, higher is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	355	342	-	MD **25 higher** (19.4 higher to 30.6 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events (final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	82/355 (23.1%)	85/342 (24.9%)	**RR 0.93** (0.71 to 1.21)	**17 fewer per 1,000** (from 72 fewer to 52 more)	⨁⨁◯◯ Low	CRITICAL
Pneumonia (respiratory tract infections, final values, lower is better)												
1	randomised trials	serious[a]	not serious	serious[d]	very serious[e]	none	53/355 (14.9%)	54/342 (15.8%)	**RR 0.95** (0.67 to 1.34)	**8 fewer per 1,000** (from 52 fewer to 54 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)

b. Downgraded by one increment due to intervention indirectness - evidence from a post-hoc analysis that included studies that treated participants with moderate-dose ICS

c. Downgraded by one increment due to the 95%CI overlapping the lower MID (0.8-1.25)

d. Downgraded by one increment due to the outcome reported in the paper not being directly relevant to the outcome listed in this review protocol (respiratory tract infections reported, not pneumonia events)

e. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

Table 9: Clinical evidence profile: low dose ICS/formoterol MART vs regular low dose ICS/LABA with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA MART	Regular low-dose ICS/LABA with SABA as needed	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	313/2156 (14.5%)	474/2180 (21.7%)	**RR 0.67** (0.59 to 0.76)	**72 fewer per 1,000** (from 89 fewer to 52 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Severe exacerbation rate (per patient year, lower is better)												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	453/2156	740/2180	**Rate ratio 0.62** (0.55 to 0.70)	-	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (final values, lower is better)												
1	randomised trials	serious[b]	not serious	not serious	very serious[c]	none	1/1049 (0.1%)	1/1042 (0.1%)	**RR 0.99** (0.06 to 15.86)	**0 fewer per 1,000** (from 1 fewer to 14 more)	⨁◯◯◯ Very low	CRITICAL
Asthma control (Asthma Control Questionnaire, scale range: 0-6, final values, lower is better)												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	956	932	-	MD **0.14 lower** (0.19 lower to 0.1 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Hospital admissions at ≥6 months (final values, lower is better)												
1	randomised trials	serious[b]	not serious	not serious	not serious	none	11/1049 (1.0%)	33/1042 (3.2%)	**RR 0.33** (0.17 to 0.65)	**21 fewer per 1,000** (from 26 fewer to 11 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (puffs per day, change scores, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA MART	Regular low-dose ICS/LABA with SABA as needed	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[a]	not serious	not serious	not serious	none	2156	2180	-	MD **0.22 lower** (0.28 lower to 0.15 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (SABA-free days, %, change scores, higher is better)												
1	randomised trials	serious[b]	not serious	not serious	not serious	none	1034	1026	-	MD **4.4 higher** (1.6 higher to 7.2 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (FEV1, litres, change scores, higher is better)												
2	randomised trials	serious[b]	not serious	not serious	not serious	none	2156	2180	-	MD **0.06 higher** (0.04 higher to 0.08 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (PEF, litres per minute, change scores, higher is better)												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	2156	2180	-	MD **6.75 higher** (4.28 higher to 9.21 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events (final values, lower is better)												
1	randomised trials	serious[b]	not serious	not serious	not serious	none	602/1049 (57.4%)	599/1042 (57.5%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1,000** (from 40 fewer to 40 more)	⨁⨁⨁◯ Moderate	CRITICAL

a. Downgraded by one increment due to concerns arising from the randomisation process (method not reported) in the majority of the evidence

b. Downgraded by one increment due to concerns arising from deviations from the intended interventions (adherence to study treatments not reported) in the majority of the evidence

c. Downgraded by two increments due to the 95%CI overlapping both the upper and lower MID (0.8-1.25)

Further step-up treatment in adults and young people aged ≥12 years with uncontrolled asthma

ICS/formoterol MART vs regular moderate/high dose ICS/LABA with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/Form MART	ICS/LABA with SABA	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
5	randomised trials	not serious	not serious	not serious	serious[a]	none	389/3508 (11.1%)	651/4640 (14.0%)	**OR 0.72** (0.63 to 0.83)	**35 fewer per 1,000** (from 47 fewer to 21 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Severe exacerbation rate (final values, lower is better)												
4	randomised trials	not serious	not serious	not serious	serious[a]	none	-/2473	-/3596	**Rate ratio 0.70** (0.61 to 0.81)	-	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (final values, lower is better)												
5	randomised trials	not serious	not serious	not serious	very serious[b]	none	2/3539 (0.1%)	3/4673 (0.1%)	not estimable	**1 fewer per 1,000** (from 1 fewer to 1 more)	⨁⨁◯◯ Low	CRITICAL
Quality of life (Asthma Quality of Life Questionnaire with standard activities, scale range: 1-7, change scores, higher is better)												
1	randomised trials	very serious[c]	not serious	serious[d]	not serious	none	1067	1076	-	MD **0.03 higher** (0.06 lower to 0.12 higher)	⨁◯◯◯ Very low	CRITICAL
Asthma control (Asthma Control Questionnaire, scale range: 1-6, final values, lower is better)												
3	randomised trials	not serious	not serious	not serious	not serious	none	2369	2381	-	MD **0.05 lower** (0.09 lower to 0)	⨁⨁⨁⨁ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/Form MART	ICS/LABA with SABA	Relative (95% CI)	Absolute (95% CI)		
Hospital admissions at ≥6 months (final values, lower is better)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	41/1285 (3.2%)	61/1294 (4.7%)	**RR 0.67** (0.46 to 0.99)	**16 fewer per 1,000** (from 25 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (puffs per day, final values, lower is better)												
4	randomised trials	not serious	very serious[e]	not serious	serious[f]	none	2317	2325	-	MD **0.51 lower** (1.14 lower to 0.11 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function (FEV1, litres, change scores, higher is better)												
1	randomised trials	very serious[c]	not serious	serious[d]	not serious	none	1067	1076	-	MD **0.03 higher** (0 to 0.06 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function (FEV1, % of predicted, final values, higher is better)												
1	randomised trials	very serious[g]	not serious	serious[h]	not serious	none	151	152	-	MD **3 higher** (1.43 lower to 7.43 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function (PEF, litres per minute, final values, higher is better)												
1	randomised trials	not serious	not serious	not serious	not serious	none	1151	1153	-	MD **0.8 lower** (4.4 lower to 2.8 higher)	⨁⨁⨁⨁ High	CRITICAL
Adverse events (final values, lower is better)												
2	randomised trials	not serious	not serious	not serious	not serious	none	530/2218 (23.9%)	550/2229 (24.7%)	**RR 0.97** (0.88 to 1.06)	**7 fewer per 1,000** (from 30 fewer to 15 more)	⨁⨁⨁⨁ High	CRITICAL

a. Downgraded by one increment due to the 95%CI overlapping one MID (0.8-1.25)

b. Downgraded by two increments: optimal information size<80% using https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html

c. Downgraded by two increments due to high risk of bias (up/down titration allowed at week 4 onwards plus addition of other asthma controller medication was allowed and study was open-label; deviation from inclusion criteria (inclusion of people with higher and lower FEV1 than pre-scpecified))

d. Downgraded by one increment due to intervention indirectness - ICS dose could be down-titrated to low-dose rather than moderate-dose at investigators discretion

e. Downgraded by two increments due to substantial heterogeneity not explained by subgroup analysis or random effects model (I sq.=97%)

f. Downgraded by one increment due to the 95%CI overlapping one MID

g. Downgraded by two increments due to concerns arising from deviations from the intended interventions (unbalanced use of oral prednisolone between study arms and no adherence monitoring for maintenance therapy included)

h. Downgraded by one increment due to population indirectness (15% of participants did not have asthma that was uncontrolled at screening)

ICS/formoterol MART vs regular moderate/high dose ICS with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/Form MART	ICS with SABA	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	238/1869 (12.7%)	388/1868 (20.8%)	**RR 0.61** (0.53 to 0.71)	**81 fewer per 1,000** (from 98 fewer to 60 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Severe exacerbation rate (final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	-/943	-/947	**Rate ratio 0.57** (0.48 to 0.68)	-	⨁⨁⨁◯ Moderate	CRITICAL
Mortality (final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	1/947 (0.1%)	2/943 (0.2%)	**RR 0.50** (0.05 to 5.48)	**1 fewer per 1,000** (from 2 fewer to 10 more)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/Form MART	ICS with SABA	Relative (95% CI)	Absolute (95% CI)		
Reliever/rescue medication use (daytime SABA use, puffs per day, final values, lower is better)												
1	randomised trials	very serious[c]	not serious	serious[d]	not serious	none	922	925	-	MD **0.3 lower** (0.37 lower to 0.23 lower)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (night time SABA use, puffs per night, final values, lower is better)												
1	randomised trials	very serious[c]	not serious	serious[d]	not serious	none	922	925	-	MD **0.15 lower** (0.2 lower to 0.1 lower)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (% SABA-free days, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	947	943	-	MD **11 higher** (8.2 higher to 13.8 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (FEV1, litres, change scores, higher is better)												
1	randomised trials	very serious[c]	not serious	serious[d]	not serious	none	922	925	-	MD **0.1 higher** (0.05 higher to 0.15 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function (PEF L/min, change scores, higher is better)												
2	randomised trials	serious[a]	not serious	not serious	serious[e]	none	1872	1869	-	MD **18.86 higher** (15.76 higher to 21.96 higher)	⨁⨁◯◯ Low	CRITICAL
Adverse events (final values, lower is better)												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	1022/1869 (54.7%)	1061/1868 (56.8%)	**RR 0.96** (0.91 to 1.02)	**23 fewer per 1,000** (from 51 fewer to 11 more)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/Form MART	ICS with SABA	Relative (95% CI)	Absolute (95% CI)		
Pneumonia (final values, lower is better)												
1	randomised trials	very serious[f]	not serious	serious[d]	serious[g]	none	158/922 (17.1%)	182/925 (19.7%)	**RR 0.87** (0.72 to 1.06)	**26 fewer per 1,000** (from 55 fewer to 12 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by one increment due to concerns arising from deviations from the intended intervention (397 protocol deviations in 309 participants)

b. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

c. Downgraded by two increments due to concerns arising from the randomisation method (not reported), deviations from the intended interventions (85% adherence to maintenance medication) and missing outcome data (attrition rates not reported)

d. Downgraded by one increment due to population indirectness (12% of participants were aged 4-11 years)

e. Downgraded by one increment due to the 95%CI overlapping one MID (published MID=18.79 L/min)

f. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended intervention (85% adherence to maintenance medication) and missing outcome data (dropout rate not reported)

g. Downgraded by one increment due to the 95%CI overlapping one MID (0.8-1.25)

Regular moderate/high dose ICS/LABA with SABA prn vs low/moderate dose ICS/LABA plus montelukast with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS/LABA plus montelukast	Relative (95% CI)	Absolute (95% CI)		
Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	30	31	-	MD **1.38 higher** (1.16 higher to 1.6 higher)	⨁⨁◯◯ Low	CRITICAL
Inflammatory markers (FeNO, ppb, final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS/LABA plus montelukast	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[b]	not serious	not serious	not serious	none	30	31	-	MD **6.75 lower** (10.25 lower to 3.25 lower)	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended intervention (open label study with no information on switching between study arms, adherence to maintenance therapy or co-interventions), measurement of the outcome (subjective outcome measure with knowledge of the intervention received) and selection of the reported result (inadequate information on analysis method used)

b. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended intervention (open label study with no information on switching between study arms, adherence to maintenance therapy or co-interventions) and selection of the reported result (inadequate information on analysis method used)

Regular low/moderate dose ICS/LABA plus LAMA with SABA prn vs regular moderate/high dose ICS/LABA with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS/LABA plus LAMA	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
2	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	292/1815 (16.1%)	328/1810 (18.1%)	**RR 0.89** (0.77 to 1.02)	**20 fewer per 1,000** (from 42 fewer to 4 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (final values, lower is better)												
3	randomised trials	very serious[a]	serious[c]	not serious	very serious[d]	none	5/2626 (0.2%)	8/2623 (0.3%)	**OR 0.63** (0.21 to 1.87)	**1 fewer per 1,000** (from 2 fewer to 3 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life (Asthma Quality of Life Questionnaire, scale range 1-7, change scores, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS/LABA plus LAMA	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	1239	1236	-	MD **0.01 lower** (0.08 lower to 0.06 higher)	⨁⨁◯◯ Low	CRITICAL
Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	33	30	-	MD **0.44 lower** (0.81 lower to 0.07 lower)	⨁⨁◯◯ Low	CRITICAL
Reliever/rescue medication use (puffs per day, change scores, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	1239	1236	-	MD **0.05 lower** (0.16 lower to 0.06 higher)	⨁⨁◯◯ Low	CRITICAL
Reliever/rescue medication use (SABA-free days, %, change scores, higher is better)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	1239	1236	-	MD **0.11 higher** (2.47 lower to 2.69 higher)	⨁⨁◯◯ Low	CRITICAL
Lung function (FEV1, mL, change scores, higher is better)												
1	randomised trials	serious[e]	not serious	not serious	not serious	none	575	574	-	MD **58 lower** (99.75 lower to 16.25 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (PEF, L/min, change scores, higher is better)												
1	randomised trials	serious[e]	not serious	not serious	not serious	none	575	574	-	MD **8.4 lower** (13.21 lower to 3.59 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events (final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS/LABA plus LAMA	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[e]	serious[f]	not serious	not serious	none	1844/2626 (70.2%)	1840/2623 (70.1%)	**RR 1.00** (0.97 to 1.04)	**0 fewer per 1,000** (from 21 fewer to 28 more)	⨁⨁◯◯ Low	CRITICAL
Pneumonia (final values, lower is better)												
3	randomised trials	very serious[a]	not serious	not serious	very serious[g]	none	32/2626 (1.2%)	24/2623 (0.9%)	not estimable	**0 fewer per 1,000** (from 10 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Inflammatory markers (FeNO, ppb, final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[h]	none	33	30	-	MD **15.63 higher** (10.89 higher to 20.37 higher)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by two increments due to concerns arising from deviations from the intended intervention (no adherence monitoring included) and missing outcome data (12% missing data with reasons for discontinuation related to participant's health status)

b. Downgraded by one increment due to the 95%CI overlapping one MID (0.8-1.25)

c. Downgraded by one increment due to visual assessment of heterogeneity

d. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

e. Downgraded by one increment due to concerns arising from deviations from the intended intervention (no adherence monitoring included)

f. Downgraded by one increment due to moderate heterogeneity (I.sq=49%)

g. Downgraded by two increments due to inadequate power (6%)

h. Downgraded by one increment due to the 95%CI overlapping one MID

Regular moderate/high dose ICS/LABA with SABA prn vs regular moderate/high dose ICS with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS with SABA	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at ≥3 months (final values, lower is better)												
10	randomised trials	very serious[a]	not serious	not serious	serious[b]	publication bias strongly suspected[c]	60/2088 (2.9%)	58/1640 (3.5%)	**RR 0.73** (0.51 to 1.04)	**10 fewer per 1,000** (from 17 fewer to 1 more)	⨁◯◯◯ Very low	CRITICAL
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
10	randomised trials	very serious[a]	not serious	not serious	not serious	none	527/4332 (12.2%)	668/3735 (17.9%)	**OR 0.70** (0.61 to 0.80)	**47 fewer per 1,000** (from 62 fewer to 30 fewer)	⨁⨁◯◯ Low	CRITICAL
Severe exacerbation rate (final values, lower is better)												
5	randomised trials	serious[d]	not serious	not serious	serious[b]	none	-/2252	-/2262	**Rate ratio 0.74** (0.65 to 0.84)	-	⨁⨁◯◯ Low	CRITICAL
Mortality (final values, lower is better)												
14	randomised trials	serious[e]	not serious	not serious	very serious[f]	none	2/5173 (0.0%)	4/4335 (0.1%)	not estimable	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Quality of life (Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)												
7	randomised trials	very serious[g]	not serious	not serious	not serious	none	2348	2173	-	MD **0.14 higher** (0.08 higher to 0.21 higher)	⨁⨁◯◯ Low	CRITICAL
Asthma control (Asthma Control Test, scale range: 5-25, mixed values, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS with SABA	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials	very serious[h]	not serious	not serious	not serious	none	1515	1377	-	MD **0.88 higher** (0.6 higher to 1.16 higher)	⨁⨁◯◯ Low	CRITICAL
Asthma control (Asthma control questionnaire-7, scale range: 0-6, change scores, lower is better)												
1	randomised trials	not serious	not serious	not serious	not serious	none	674	699	-	MD **0.23 lower** (0.3 lower to 0.16 lower)	⨁⨁⨁⨁ High	CRITICAL
Hospital admissions at ≥6 months (final values, lower is better)												
2	randomised trials	serious[d]	serious[i]	not serious	very serious[i]	none	9/1412 (0.6%)	11/1110 (1.0%)	**RR 0.46** (0.07 to 2.84)	**5 fewer per 1,000** (from 9 fewer to 18 more)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (puffs per day, change scores, lower is better)												
8	randomised trials	very serious[h]	not serious	not serious	not serious	none	1410	992	-	MD **0.49 lower** (0.62 lower to 0.36 lower)	⨁⨁◯◯ Low	CRITICAL
Reliever/rescue medication use (reliever free days or % of days, change scores, higher is better)												
9	randomised trials	very serious[a]	serious[i]	not serious	not serious	none	1739	1817	-	SMD **0.28 SD higher** (0.17 higher to 0.38 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function (FEV1, litres, mixed values, higher is better)												
12	randomised trials	very serious[a]	serious[i]	not serious	not serious	none	4114	3677	-	MD **0.11 higher** (0.09 higher to 0.12 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS with SABA	Relative (95% CI)	Absolute (95% CI)		
Lung function (FEV1, % of predicted, mixed values, higher is better)												
6	randomised trials	very serious[k]	not serious	not serious	serious[l]	none	863	889	-	MD **0.38 higher** (0 to 0.76 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function (PEF, L/min, mixed values, higher is better)												
16	randomised trials	very serious[a]	serious[l]	not serious	not serious	none	3329	2612	-	MD **24.31 higher** (19.83 higher to 28.78 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events (final values, lower is better)												
16	randomised trials	serious[m]	not serious	not serious	not serious	none	3491/5955 (58.6%)	2720/4758 (57.2%)	**RR 0.97** (0.94 to 1.00)	**17 fewer per 1,000** (from 34 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Pneumonia (including respiratory tract infections, final values, lower is better)												
11	randomised trials	serious[e]	not serious	not serious	very serious[f]	none	97/4427 (2.2%)	76/2972 (2.6%)	RD -0.01 (-0.02 to 0.00)	**10 more per 1,000** (from 0 fewer to 20 more)	⨁◯◯◯ Very low	CRITICAL
Adrenal insufficiency (cortisol/creatinine ratio, change scores, lower is better)												
1	randomised trials	very serious[n]	not serious	not serious	serious[l]	none	100	101	-	MD **16.86 higher** (7.37 higher to 26.35 higher)	⨁◯◯◯ Very low	CRITICAL
Adrenal insufficiency (serum cortisol, 0-24h AUC, change scores, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS with SABA	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[o]	not serious	not serious	serious[l]	none	29	28	-	MD **0.2 higher** (0.02 higher to 0.38 higher)	⨁◯◯◯ Very low	CRITICAL

Adrenal insufficiency (morning cortisol <5 mcg/dL, final values, lower is better)

1	randomised trials	very serious[p]	not serious	not serious	very serious[i]	none	1/81 (1.2%)	2/81 (2.5%)	**RR 0.50** (0.05 to 5.41)	**12 fewer per 1,000** (from 23 fewer to 109 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by two increments because the majority of evidence is at high risk of bias (no adherence monitoring reported or low; randomisation method not reported; high dropout rate with no information on rates per group or reasons for discontinuation or reasons for discontinuation related to participant's health status).

b. Downgraded by one increment because 95% CI crosses one MID (0.8-1.25)

c. Asymmetry detected in funnel plot suggests publication bias.

d. Downgraded by one increment due concerns about risk of bias in the majority of studies due to deviations from the intended interventions (no information on adherence to interventions)

e. Downgraded by one increment due to some concerns about risk of bias in the majority of studies (due to no adherence monitoring; unclear information about randomisation and high dropout rate with reasons for discontinuation related to participant's health status)

f. Downgraded by two increments: optimal information size<80% using https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html

g. Downgraded by two increments because the majority of evidence is at high risk of bias (Adherence not reported or low; high dropout rate and reasons for discontinuation related to participant's health status

h. Downgraded by two increments because the majority of evidence is at high risk of bias (Adherence not reported or low; high dropout rate and reasons for discontinuation related to participant's health status; randomisation method not reported)

i. Downgraded by one increment due to unexplained heterogeneity

j. Downgraded by two increments because 95% CI crosses both MIDs (0.8-1.25)

k. Downgrade by two increments because the majority of evidence is at high risk of bias (randomisation method not reported; includes an unblinded trial with no information on switching between groups or co-interventions; adherence not reported or 86.7%; high dropout rate with reasons related to participant's health status or no information of rates per study arm.

l. Downgraded by one increment because 95%cI crosses one MID (calculated as baseline SD (of intervention + control groups/2)/2=0.5)

m. Downgraded by one increment due to some concerns about risk of bias in the majority of studies (due to no adherence monitoring; lack of information about randomisation and high dropout rate with reasons for discontinuation related to participant's health status)

n. Downgraded by two increments because the study is at high risk of bias (randomisation method not reported and no adherence monitoring)

o. Downgraded by two increments because the study was at high risk of bias (randomisation method not reported and no information on dropout rate from 15% subset of participants who had cortisol measured)

p. Downgraded by two increments because the study was at high risk of bias (randomisation method not reported, 22% missing data, 11% difference in missing data rates between study arms and reasons for discontinuation related to participant's health status)

Regular moderate/high dose ICS/LABA with SABA prn vs regular low dose ICS plus montelukast with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS plus montelukast	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at 3-5 months (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	26/476 (5.5%)	23/472 (4.9%)	**RR 1.12** (0.65 to 1.94)	**6 more per 1,000** (from 17 fewer to 46 more)	⨁◯◯◯ Very low	CRITICAL
Severe exacerbation rate (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	27/476	24/472	**Rate ratio 1.12** (0.64 to 1.93)	-	⨁◯◯◯ Very low	CRITICAL
Mortality (final values, lower is better)												
1	randomised trials	very serious[d]	not serious	very serious[e]	very serious[f]	none	0/185 (0.0%)	0/176 (0.0%)	**RD 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life (Asthma Quality of Life Questionnaire, scale range 1-7, mixed values, higher is better)												
1	randomised trials	very serious[g]	not serious	very serious[e]	not serious	none	181	169	-	MD **0.01 lower** (0.24 lower to 0.22 higher)	⨁◯◯◯ Very low	CRITICAL
Quality of life (EQ-5D, scale range: 0-1, final values, higher is better)												
1	randomised trials	very serious[g]	not serious	very serious[e]	very serious[h]	none	170	160	-	MD **0.01 lower** (0.07 lower to 0.05 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS plus montelukast	Relative (95% CI)	Absolute (95% CI)		
Asthma control (Asthma Control Questionnaire, scale range: 0-6, final values, lower is better)												
1	randomised trials	very serious[g]	not serious	very serious[e]	not serious	none	181	169	-	MD **0.03 higher** (0.17 lower to 0.23 higher)	⨁◯◯◯ Very low	CRITICAL
Hospital admissions at ≥6 months (final values, lower is better)												
1	randomised trials	very serious[d]	not serious	very serious[e]	very serious[c]	none	5/185 (2.7%)	3/176 (1.7%)	**RR 1.59** (0.38 to 6.54)	**10 more per 1,000** (from 11 fewer to 94 more)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (puffs per day, change scores, lower is better)												
1	randomised trials	very serious[a]	not serious	serious[b]	not serious	none	452	448	-	MD **0.24 lower** (0.53 lower to 0.05 higher)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (night time reliever use, final values, lower is better)												
1	randomised trials	very serious[i]	not serious	very serious[e]	not serious	none	87	75	-	MD **0.06 lower** (0.36 lower to 0.24 higher)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (daytime reliever use, final values, lower is better)												
1	randomised trials	very serious[i]	not serious	very serious[e]	not serious	none	95	84	-	MD **0.4 lower** (1 lower to 0.2 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function (PEF, L/min, mixed values, higher is better)												
1	randomised trials	very serious[d]	not serious	very serious[e]	serious[j]	none	98	83	-	MD **24.2 higher** (5.6 lower to 54 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS plus montelukast	Relative (95% CI)	Absolute (95% CI)		
Pneumonia (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	0/476 (0.0%)	1/472 (0.2%)	**OR 0.13** (0.00 to 6.76)	**2 fewer per 1,000** (from -- to 12 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended intervention (switching rates between study groups not reported and adherence not monitored) and selection of the reported result (inadequate information on statistical methods used)

b. Downgraded by one increment due to intervention indirectness - participants had interventions added on to their current ICS therapy which could have been low, moderate or high dose

c. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

d. Downgraded by two increments due to concerns arising from deviations from the intended intervention (adherence monitoring not included), and missing outcome data (>10% missing with reasons for discontinuation related to participant's health status)

e. Downgraded by two increments due to intervention indirectness - participants could have been treated with montelukast or zafirlukast with no information on number given each, and flexible ICS dosing with the possibility of removal of regular ICS

f. Downgraded due to inadequate power

g. Downgraded by two increments due to concerns arising from deviations from the intended intervention (86% adherence to maintenance therapy and use of additional therapies in 31% of participants) and measurement of the outcome (subjective outcome measure assessed in an open label study)

h. Downgraded by two increments due to the 95%CI overlapping both MIDs

i. Downgraded by two increments due to concerns arising from deviations from the intended intervention (86% adherence to maintenance therapy and use of additional therapies in 31% of participants)

j. Downgraded by one increment due to the 95%CI overlapping one MID

Regular low/moderate dose ICS/LABA plus montelukast with SABA prn vs regular low/moderate dose ICS/LABA plus LAMA with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA plus montelukast	ICS/LABA plus LAMA	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at >6 months (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	6/28 (21.4%)	5/29 (17.2%)	**RR 1.24** (0.43 to 3.61)	**41 more per 1,000** (from 98 fewer to 450 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life (Asthma Quality of Life Questionnaire, symptom domain, scale range: 0-7, change scores, higher is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	28	29	-	MD **0** (0.52 lower to 0.52 higher)	⨁◯◯◯ Very low	CRITICAL
Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)												
1	randomised trials	very serious[c]	not serious	not serious	not serious	none	31	33	-	MD **0.94 lower** (1.33 lower to 0.55 lower)	⨁⨁◯◯ Low	CRITICAL
Lung function (FEV1, % of predicted, change scores, higher is better)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	28	29	-	MD **3 lower** (4.85 lower to 1.15 lower)	⨁⨁◯◯ Low	CRITICAL
Inflammatory markers (FeNO, ppb, mixed values, lower is better)												
2	randomised trials	very serious[a]	serious[d]	not serious	serious[e]	none	59	62	-	MD **5.4 lower** (11.29 lower to 0.5 higher)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by two increments due to concerns arising from selection of the reported result (inadequate information on statistical methods used), deviations from the intended intervention (adherence not monitored), missing outcome data (15% missing with no information on dropout rates per arm or reasons for discontinuation)

b. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

c. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended intervention (open label study with no information on switching between study arms, adherence to maintenance therapy or co-interventions), measurement of the outcome (subjective outcome measure with knowledge of the intervention received) and selection of the reported result (inadequate information on analysis method used)

d. Downgraded by one increment due to unexplained heterogeneity

e. MID calculated as baseline SD (of intervention + control groups in both studies/4)/2 = 6.67

Regular moderate/high dose ICS/LABA with SABA prn vs regular low/moderate dose ICS plus LAMA with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS plus LAMA	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at 3-5 months (final values, lower is better)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	17/134 (12.7%)	16/128 (12.5%)	**RR 1.01** (0.54 to 1.92)	**1 more per 1,000** (from 57 fewer to 115 more)	⨁◯◯◯ Very low	CRITICAL
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
1	randomised trials	serious[c]	not serious	serious[d]	serious[e]	none	34/541 (6.3%)	53/1036 (5.1%)	**RR 1.23** (0.81 to 1.87)	**12 more per 1,000** (from 10 fewer to 45 more)	⨁◯◯◯ Very low	CRITICAL
Mortality (final values, lower is better)												
1	randomised trials	serious[c]	not serious	serious[f]	very serious[a]	none	0/110 (0.0%)	0/215 (0.0%)	**RD 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life (Mini Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	134	128	-	MD **0.15 higher** (0.03 lower to 0.33 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS plus LAMA	Relative (95% CI)	Absolute (95% CI)		
Hospital admissions at ≥3 months (final values, lower is better)												
1	randomised trials	not serious	not serious	serious[a]	serious[e]	none	4/134 (3.0%)	0/128 (0.0%)	**OR 7.23** (1.01 to 51.93)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Hospital admissions at ≥6 months (final values, lower is better)												
1	randomised trials	serious[c]	not serious	serious[f]	very serious[b]	none	1/110 (0.9%)	5/215 (2.3%)	**RR 0.39** (0.05 to 3.30)	**14 fewer per 1,000** (from 22 fewer to 53 more)	⨁◯◯◯ Very low	CRITICAL
Reliever/rescue medication use (puffs per day, change scores, lower is better)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	134	128	-	MD **0.2 lower** (0.72 lower to 0.32 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (FEV1, litres, change scores, higher is better)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	134	128	-	MD **0.02 higher** (0.06 lower to 0.1 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (PEF, L/min, change scores, higher is better)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	134	128	-	MD **0.02 lower** (0.1 lower to 0.06 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events (final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/LABA with SABA	ICS plus LAMA	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[c]	not serious	serious[d]	not serious	none	341/675 (50.5%)	633/1164 (54.4%)	**RR 0.96** (0.87 to 1.05)	**22 fewer per 1,000** (from 71 fewer to 27 more)	⨁⨁◯◯ Low	CRITICAL
Pneumonia (including respiratory tract infections, final values, lower is better)												
2	randomised trials	serious[c]	not serious	very serious[h]	very serious[b]	none	7/675 (1.0%)	16/1164 (1.4%)	**RR 0.69** (0.29 to 1.66)	**4 fewer per 1,000** (from 10 fewer to 9 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by one increment due to population indirectness (8% of participants had been treated with oral xanthines or leukotriene modifiers prior to study)

b. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

c. Downgraded by one increment due to concerns arising from deviations from the intended intervention (adherence monitoring not included)

d. Downgraded by one increment due to population indirectness (9% of participants had been treated with leukotriene modifiers prior to study)

e. Downgraded by one increment due to the 95%CI overlapping one MID (0.8-1.25)

f. Downgraded by one increment due to population indirectness (in primary study 8% of participants had been treated with oral xanthines or leukotriene modifiers prior to study, not reported in paper informing this analysis)

g. Downgraded by two increments due to inadequate power (not estimable)

h. Downgraded by one increment due to population indirectness (9% of participants had been treated with leukotriene modifiers prior to study) and one due to outcome indirectness (assessed respiratory tract infections, not pneumonia as specified)

Regular moderate/high dose ICS with SABA prn vs Regular low/moderate dose ICS plus montelukast with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS with SABA	ICS plus montelukast	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at 3-5 months (final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS with SABA	ICS plus montelukast	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22/511 (4.3%)	14/518 (2.7%)	**RR 1.58** (0.83 to 3.02)	**16 more per 1,000** (from 5 fewer to 55 more)	⨁⨁◯◯ Low	CRITICAL
Severe exacerbation rate (final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	20/70	9/70	**Rate ratio 0.45** (0.20 to 0.99)	-	⨁⨁◯◯ Low	CRITICAL
Quality of life (Asthma quality of life questionnaire, scale range: 1-7, final values, higher is better)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	28	24	-	MD **0.24 lower** (0.77 lower to 0.29 higher)	⨁◯◯◯ Very low	CRITICAL
Asthma control (Asthma Control Test, scale range: 5-25, final values, higher is better)												
1	randomised trials	very serious[d]	not serious	not serious	not serious	none	70	70	-	MD **0.5 lower** (2.04 lower to 1.04 higher)	⨁⨁◯◯ Low	CRITICAL
Reliever/rescue medication use (puffs per day, change scores, lower is better)												
1	randomised trials	very serious[e]	not serious	not serious	not serious	none	441	448	-	MD **0.19 higher** (0.03 higher to 0.35 higher)	⨁⨁◯◯ Low	CRITICAL
Lung function (FEV1, % of predicted, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	70	70	-	MD **2.94 lower** (6.23 lower to 0.35 higher)	⨁⨁◯◯ Low	CRITICAL
Lung function (PEF, L/minute, change scores, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS with SABA	ICS plus montelukast	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[e]	not serious	not serious	not serious	none	469	472	-	MD **3 lower** (12.02 lower to 6.01 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Adverse events (final values, lower is better)

2	randomised trials	serious[e]	not serious	not serious	serious[b]	none	215/479 (44.9%)	194/485 (40.0%)	**RR 1.12** (0.97 to 1.29)	**48 more per 1,000** (from 12 fewer to 116 more)	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by one increment due to some concerns of risk of bias (unclear if missing data and/or if ITT or PP analyses used; no pre-specified analyses in a protocol)

b. Downgraded by one increment due to the 95%CI overlapping one MID

c. Downgraded by two increments due to concerns arising from the randomisation process (method not reported), deviations from the intended interventions (adherence to montelukast and placebo treatments was 77% and 84%, respectively) and missing outcome data (paired data reported only)

d. Downgrade by two increments due to the being at high risk of bias (self-reported outcome and open-label study; unclear if missing data and/or if ITT or PP analyses used; no pre-specification of analyses in a protocol)

e. Downgraded by one increment due to concerns arising from a lack of clarity surrounding the randomisation process (method not reported) and deviations from the intended interventions (adherence to interventions not reported)

Children aged 5-11 years

Regular paediatric moderate/high dose ICS/LABA with SABA prn vs regular paediatric moderate/high dose ICS with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular paediatric moderate/high dose ICS/LABA with SABA prn	Regular paediatric moderate/high dose ICS with SABA prn	Relative (95% CI)	Absolute (95% CI)		

Severe asthma exacerbations at 3-5 months (final values, lower is better)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular paediatric moderate/high dose ICS/LABA with SABA prn	Regular paediatric moderate/high dose ICS with SABA prn	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[a]	not serious	not serious	serious[b]	none	25/434 (5.8%)	22/345 (6.4%)	**RR 0.70** (0.40 to 1.23)	**19 fewer per 1,000** (from 38 fewer to 15 more)	⨁⨁◯◯ Low	CRITICAL
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
3	randomised trials	serious[c]	not serious	not serious	serious[b]	none	49/210 (23.3%)	26/197 (13.2%)	**RR 1.72** (1.12 to 2.63)	**95 more per 1,000** (from 16 more to 215 more)	⨁⨁◯◯ Low	CRITICAL
Severe exacerbation rate (events per person year, lower is better)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	52/117	32/106	**Rate ratio 1.47** (0.95 to 2.29)	-	⨁⨁◯◯ Low	CRITICAL
Mortality (final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	0/183 (0.0%)	0/90 (0.0%)	**RD 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more)	⨁⨁◯◯ Low	CRITICAL
Quality of life (PAQLQ, scale range: 1-7, change scores, lower is better)												
2	randomised trials	very serious[e]	not serious	not serious	not serious	none	123	65	-	MD **0.14 higher** (0.15 lower to 0.43 higher)	⨁⨁◯◯ Low	CRITICAL
Hospital admissions (final values, lower is better)												
2	randomised trials	very serious[f]	very serious[g]	not serious	very serious[h]	none	6/138 (4.3%)	7/74 (9.5%)	**OR 0.42** (0.13 to 1.36)	**53 fewer per 1,000** (from 81 fewer to 30 more)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular paediatric moderate/high dose ICS/LABA with SABA prn	Regular paediatric moderate/high dose ICS with SABA prn	Relative (95% CI)	Absolute (95% CI)		
Reliever/rescue medication use (puffs per day, mixed values, lower is better)												
2	randomised trials	serious[c]	not serious	not serious	not serious	none	300	196	-	MD **0.01 puffs per day higher** (0.1 lower to 0.11 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (reliever-free days, % of days, final values, higher is better)												
1	randomised trials	serious[c]	not serious	not serious	not serious	none	117	106	-	MD **3.5 % higher** (15.61 lower to 22.61 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (PEF, % of predicted, final values, higher is better)												
1	randomised trials	serious[i]	not serious	not serious	not serious	none	78	80	-	MD **2.2 % higher** (2.74 lower to 7.14 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (PEF, L/min, mixed values, higher is better)												
3	randomised trials	serious[c]	not serious	not serious	not serious	none	416	331	-	MD **5.35 L/min higher** (2.3 higher to 8.39 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (FEV1, % of predicted, mixed values, higher is better)												
2	randomised trials	serious[i]	serious[g]	not serious	serious[b]	none	91	88	-	MD **6.38 % higher** (8.15 lower to 20.91 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events (final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular paediatric moderate/high dose ICS/LABA with SABA prn	Regular paediatric moderate/high dose ICS with SABA prn	Relative (95% CI)	Absolute (95% CI)		
8	randomised trials	serious[i]	not serious	not serious	not serious	none	521/1190 (43.8%)	353/820 (43.0%)	**RR 1.08** (0.98 to 1.19)	**34 more per 1,000** (from 9 fewer to 82 more)	⨁⨁⨁◯ Moderate	CRITICAL
Pneumonia (including lower respiratory tract infections, final values, lower is better)												
3	randomised trials	serious[k]	not serious	not serious	not serious	none	4/341 (1.2%)	3/271 (1.1%)	**RD 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adrenal insufficiency (number of participants with morning cortisol <400 nmol/L, final values, lower is better)												
1	randomised trials	serious[c]	not serious	not serious	very serious[h]	none	1/55 (1.8%)	3/41 (7.3%)	**RR 0.25** (0.03 to 2.30)	**55 fewer per 1,000** (from 71 fewer to 95 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by one increment due to concerns arising from deviations from the intended interventions (adherence not reported) and selection of the reported result (inadequate detail of pre-specified analysis)

b. Downgraded by one increment due to the 95%CI overlapping one MID

c. Downgraded by one increment due to concerns arising from deviations from the intended interventions (adherence not reported)

d. Downgraded by one increment based on inadequate sample size

e. Downgraded by two increments due to concerns arising from deviations from the intended interventions (adherence not reported and potential concomitant medication administration), measurement of the outcome (open-label study design with subjective outcome measure) and selection of the reported result (inadequate detail of pre-specified analysis)

f. Downgraded by two increments due to concerns arising from deviations from the intended interventions (adherence not reported and potential concomitant medication administration) and selection of the reported result (inadequate detail of pre-specified analysis)

g. Downgraded by two increments due to substantial heterogeneity

h. Downgraded by two increments due to the 95%CI overlapping both MIDs

i. Downgraded by one increment due to concerns arising from the randomisation process (method not reported)

j. Downgraded by one increment due to concerns arising from various elements of the Risk of Bias tool (randomisation method not reported, adherence not reported, inadequate detail of pre-specified analyses)

k. Downgraded by one increment due to concerns arising from the randomisation process (method not reported) in the majority of the evidence

ICS/formoterol MART vs regular paediatric moderate/high dose ICS/LABA with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/Formoterol MART	Regular paediatric moderate/high dose ICS/LABA with SABA prn	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	10/118 (8.5%)	36/117 (30.8%)	**RR 0.28** (0.14 to 0.53)	**222 fewer per 1,000** (from 265 fewer to 145 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Severe exacerbation rate (events per person year, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	11/118	52/117	**Rate ratio 4.77** (2.49 to 9.14)	-	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (puffs per day, final values, lower is better												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	118	117	-	MD **0.18 puffs per day lower** (0.35 lower to 0.01 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (reliever-free days, % of days, final values, higher is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	118	117	-	MD **1.9 % higher** (3.36 lower to 7.16 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (PEF, L/min, final values, higher is better)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	118	117	-	MD **13 L/min higher** (7.72 lower to 33.72 higher)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/Formoterol MART	Regular paediatric moderate/high dose ICS/LABA with SABA prn	Relative (95% CI)	Absolute (95% CI)		
Adverse events (final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	2/118 (1.7%)	16/117 (13.7%)	**RR 0.12** (0.03 to 0.53)	**120 fewer per 1,000** (from 133 fewer to 64 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Pneumonia (final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	0/118 (0.0%)	2/117 (1.7%)	**OR 0.13** (0.01 to 2.14)	**15 fewer per 1,000** (from 17 fewer to 19 more)	⨁◯◯◯ Very low	CRITICAL
Adrenal insufficiency (number of participants with morning cortisol <400 nmol/L, final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	2/51 (3.9%)	1/55 (1.8%)	**RR 2.16** (0.20 to 23.07)	**21 more per 1,000** (from 15 fewer to 401 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by one increment due to concerns arising from deviations from the intended interventions (adherence not reported)

b. Downgraded by one increment due to the 95%CI overlapping one MID threshold

c. Downgraded by two increments due to the 95%CI overlapping both MIDs

ICS/formoterol MART vs regular paediatric moderate/high dose ICS with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/formoterol MART	Regular paediatric moderate/high dose ICS plus SABA prn	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	10/118 (8.5%)	21/106 (19.8%)	**RR 0.43** (0.21 to 0.87)	**113 fewer per 1,000** (from 157 fewer to 26 fewer)	⨁⨁◯◯ Low	CRITICAL
Severe exacerbation rate (events per person year, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	11/118	32/106	**Rate ratio 3.24** (1.63 to 6.42)	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (puffs per day, final values, lower is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	118	106	-	MD **0.16 puffs per day lower** (0.35 lower to 0.03 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Reliever/rescue medication use (reliever-free days, % of days, final values, higher is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	118	106	-	MD **5.4 % higher** (1.38 lower to 12.18 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Lung function (PEF, L/min, final values, higher is better)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	118	106	-	MD **17 L/min higher** (6.4 higher to 27.6 higher)	⨁⨁◯◯ Low	CRITICAL
Adverse events (final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS/formoterol MART	Regular paediatric moderate/high dose ICS plus SABA prn	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	2/118 (1.7%)	5/106 (4.7%)	**RR 0.36** (0.07 to 1.81)	**30 fewer per 1,000** (from 44 fewer to 38 more)	⨁◯◯◯ Very low	CRITICAL

Pneumonia (final values, lower is better)

1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	0/109 (0.0%)	0/92 (0.0%)	not estimable	**0 fewer per 1,000** (from 20 fewer to 20 more)	⨁⨁◯◯ Low	CRITICAL

Adrenal insufficiency (number of participants with morning cortisol <400 nmol/L, final values, lower is better)

1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	2/51 (3.9%)	3/41 (7.3%)	**RR 0.54** (0.09 to 3.06)	**34 fewer per 1,000** (from 67 fewer to 151 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by one increment due to concerns arising from deviations from the intended interventions (adherence not reported)

b. Downgraded by one increment due to the 95%CI overlapping one MID

c. Downgraded by two increments due to the 95%CI overlapping both MIDs

d. Downgraded by one increment due to an inadequate sample size to appropriately power the analysis

Regular paediatric moderate/high dose ICS with SABA prn vs regular paediatric moderate dose ICS plus montelukast with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular paediatric moderate/high dose ICS with SABA prn	Regular paediatric moderate dose ICS with montelukast plus SABA prn	Relative (95% CI)	Absolute (95% CI)		

Severe asthma exacerbations at ≥6 months (final values, lower is better)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular paediatric moderate/high dose ICS with SABA prn	Regular paediatric moderate dose ICS with montelukast plus SABA prn	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	1/11 (9.1%)	1/12 (8.3%)	**RR 1.09** (0.08 to 15.41)	**8 more per 1,000** (from 77 fewer to 1,000 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life (Paediatric Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)												
1	randomised trials	very serious[d]	not serious	serious[b]	serious[e]	none	10	12	-	MD **0.55 lower** (1.56 lower to 0.46 higher)	⨁◯◯◯ Very low	CRITICAL
Hospital admissions (final values, lower is better)												
1	randomised trials	very serious[d]	not serious	serious[b]	very serious[f]	none	0/18 (0.0%)	0/19 (0.0%)	not estimable	**0 fewer per 1,000** (from 100 fewer to 100 more)	⨁◯◯◯ Very low	CRITICAL
Lung function (FEV1, % of predicted, change scores, higher is better)												
1	randomised trials	very serious[d]	not serious	serious[b]	very serious[c]	none	8	9	-	MD **4.43 % of predicted lower** (18.03 lower to 9.17 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events (final values, lower is better)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[e]	none	17/19 (89.5%)	18/21 (85.7%)	**RR 1.04** (0.83 to 1.32)	**34 more per 1,000** (from 146 fewer to 274 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by one increment due to concerns arising from missing outcome data (missing data rate greater than event rate)

b. Downgraded by one increment due to population indirectness (age variance overlaps upper limit of age strata)

c. Downgraded by two increments due to the 95%CI overlapping both MIDs

d. Downgraded by two increments due to concerns arising from missing outcome data (missing data rate greater than event rate, and disproportionate rate of missingness between arms)

e. Downgraded by one increment due to the 95%CI overlapping one MID

f. Downgraded by two increments due to inadequate sample size to appropriately power the analysis

Regular paediatric moderate/high dose ICS/LABA with SABA prn vs regular paediatric moderate dose ICS plus montelukast with SABA prn

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular paediatric moderate/high dose ICS/LABA plus SABA prn	Regular paediatric moderate dose ICS plus montelukast with SABA prn	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at ≥6 months (final values, lower is better)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	5/15 (33.3%)	1/12 (8.3%)	**RR 4.00** (0.54 to 29.80)	**250 more per 1,000** (from 38 fewer to 1,000 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life (Paediatric Asthma Quality of Life Questionnaire, scale range: 1-7, change scores, higher is better)												
1	randomised trials	very serious[d]	not serious	serious[b]	very serious[c]	none	15	12	-	MD **0.74 lower** (2.07 lower to 0.59 higher)	⨁◯◯◯ Very low	CRITICAL
Hospital admissions (final values, lower is better)												
1	randomised trials	very serious[d]	not serious	serious[b]	very serious[e]	none	0/17 (0.0%)	0/19 (0.0%)	not estimable	**0 fewer per 1,000** (from 100 fewer to 100 more)	⨁◯◯◯ Very low	CRITICAL
Lung function (FEV1, % of predicted, change scores, higher is better)												
1	randomised trials	very serious[d]	not serious	serious[b]	serious[f]	none	13	9	-	MD **10.99 higher** (3.92 lower to 25.9 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events (final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular paediatric moderate/high dose ICS/LABA plus SABA prn	Regular paediatric moderate dose ICS plus montelukast with SABA prn	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	serious[f]	none	18/23 (78.3%)	18/21 (85.7%)	**RR 0.91** (0.69 to 1.20)	**77 fewer per 1,000** (from 266 fewer to 171 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by one increment due to concerns arising from missing outcome data (missing data rate greater than event rate)

b. Downgraded by one increment due to population indirectness (age variance overlaps upper limit of age strata)

c. Downgraded by two increments due to the 95%CI overlapping both MIDs

d. Downgraded by two increments due to concerns arising from missing outcome data (missing data rate greater than event rate, and disproportionate rate of missingness between arms)

e. Downgraded by two increments due to inadequate sample size to appropriately power the analysis

f. Downgraded by one increment due to the 95%CI overlapping one MID

Children under 5 years

Table 16: Clinical evidence profile: regular ICS vs as-needed ICS/SABA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular ICS	as-needed ICS/SABA	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at 3-5 months (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	47/249 (18.9%)	69/250 (27.6%)	**RR 0.68** (0.49 to 0.95)	**88 fewer per 1,000** (from 141 fewer to 14 fewer)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular ICS	as-needed ICS/SABA	Relative (95% CI)	Absolute (95% CI)		
Hospital admissions at 3-5 months (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	0/249 (0.0%)	1/250 (0.4%)	**OR 0.14** (0.00 to 6.85)	**3 fewer per 1,000** (from -- to 23 more)	⨁◯◯◯ Very low	CRITICAL
Pneumonia (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	1/249 (0.4%)	0/250 (0.0%)	**OR 7.42** (0.15 to 373.89)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by two increments due to concerns arising from the randomisation process and missing outcome data

b. Downgraded by one increment due to the 95%CI overlapping the lower MID (0.8-1.25)

c. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

Table 17: Clinical evidence profile: regular ICS vs regular montelukast

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular ICS	regular montelukast	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at 3-5 months (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	47/249 (18.9%)	87/256 (34.0%)	**RR 0.56** (0.41 to 0.76)	**150 fewer per 1,000** (from 201 fewer to 82 fewer)	⨁⨁◯◯ Low	CRITICAL
Severe asthma exacerbations at ≥6 months (final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular ICS	regular montelukast	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[b]	not serious	not serious	serious[c]	none	23/105 (21.9%)	36/97 (37.1%)	**RR 0.59** (0.38 to 0.92)	**152 fewer per 1,000** (from 230 fewer to 30 fewer)	⨁◯◯◯ Very low	CRITICAL
Mortality (final values, lower is better)												
1	randomised trials	very serious[b]	not serious	not serious	very serious[d]	none	0/105 (0.0%)	0/97 (0.0%)	not estimable	**0 fewer per 1,000** (from 20 fewer to 20 more)	⨁◯◯◯ Very low	CRITICAL
Hospital admissions at 3-5 months (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	0/249 (0.0%)	6/256 (2.3%)	**OR 0.14** (0.03 to 0.68)	**20 fewer per 1,000** (from 23 fewer to 7 fewer)	⨁⨁◯◯ Low	CRITICAL
Reliever/rescue medication use (puffs per day, change scores, lower is better)												
1	randomised trials	very serious[b]	not serious	not serious	not serious	none	104	97	-	MD **0.03 puffs per day higher** (0.28 lower to 0.34 higher)	⨁⨁◯◯ Low	CRITICAL
Lung function (PEF, L/min, change scores, higher is better)												
1	randomised trials	very serious[b]	not serious	not serious	not serious	none	79	67	-	MD **7.1 L/min higher** (0.43 lower to 14.63 higher)	⨁⨁◯◯ Low	CRITICAL
Adverse events (final values, lower is better)												
1	randomised trials	very serious[b]	not serious	not serious	not serious	none	84/105 (80.0%)	80/97 (82.5%)	**RR 0.97** (0.85 to 1.11)	**25 fewer per 1,000** (from 124 fewer to 91 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regular ICS	regular montelukast	Relative (95% CI)	Absolute (95% CI)		
Pneumonia (final values, lower is better)												
2	randomised trials	very serious[b]	not serious	not serious	very serious[e]	none	5/354 (1.4%)	6/353 (1.7%)	**OR 0.77** (0.23 to 2.57)	**4 fewer per 1,000** (from 13 fewer to 26 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by two increments due to concerns arising from the randomisation process and missing outcome data

b. Downgraded by two increments due to concerns arising from the randomisation process, deviations from the intended interventions and missing outcome data

c. Downgraded by one increment due to the 95%CI overlapping one MID

d. Downgraded by two increments due to inadequate sample size (power <80%)

e. Downgraded by two increments due to the 95%CI overlapping both MIDs

Table 18: Clinical evidence profile: as-needed ICS/SABA vs regular montelukast

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	As-needed ICS/SABA	regular montelukast	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations at 3-5 months (final values, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	69/250 (27.6%)	87/256 (34.0%)	**RR 0.81** (0.62 to 1.06)	**65 fewer per 1,000** (from 129 fewer to 20 more)	⨁◯◯◯ Very low	CRITICAL
Hospital admissions at 3-5 months (final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	As-needed ICS/SABA	regular montelukast	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	1/250 (0.4%)	6/256 (2.3%)	**RR 0.17** (0.02 to 1.41)	**19 fewer per 1,000** (from 23 fewer to 10 more)	⨁◯◯◯ Very low	CRITICAL

Pneumonia (final values, lower is better)

1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	0/250 (0.0%)	0/256 (0.0%)	not estimable	**0 fewer per 1,000** (from 10 fewer to 10 more)	⨁◯◯◯ Very low	CRITICAL

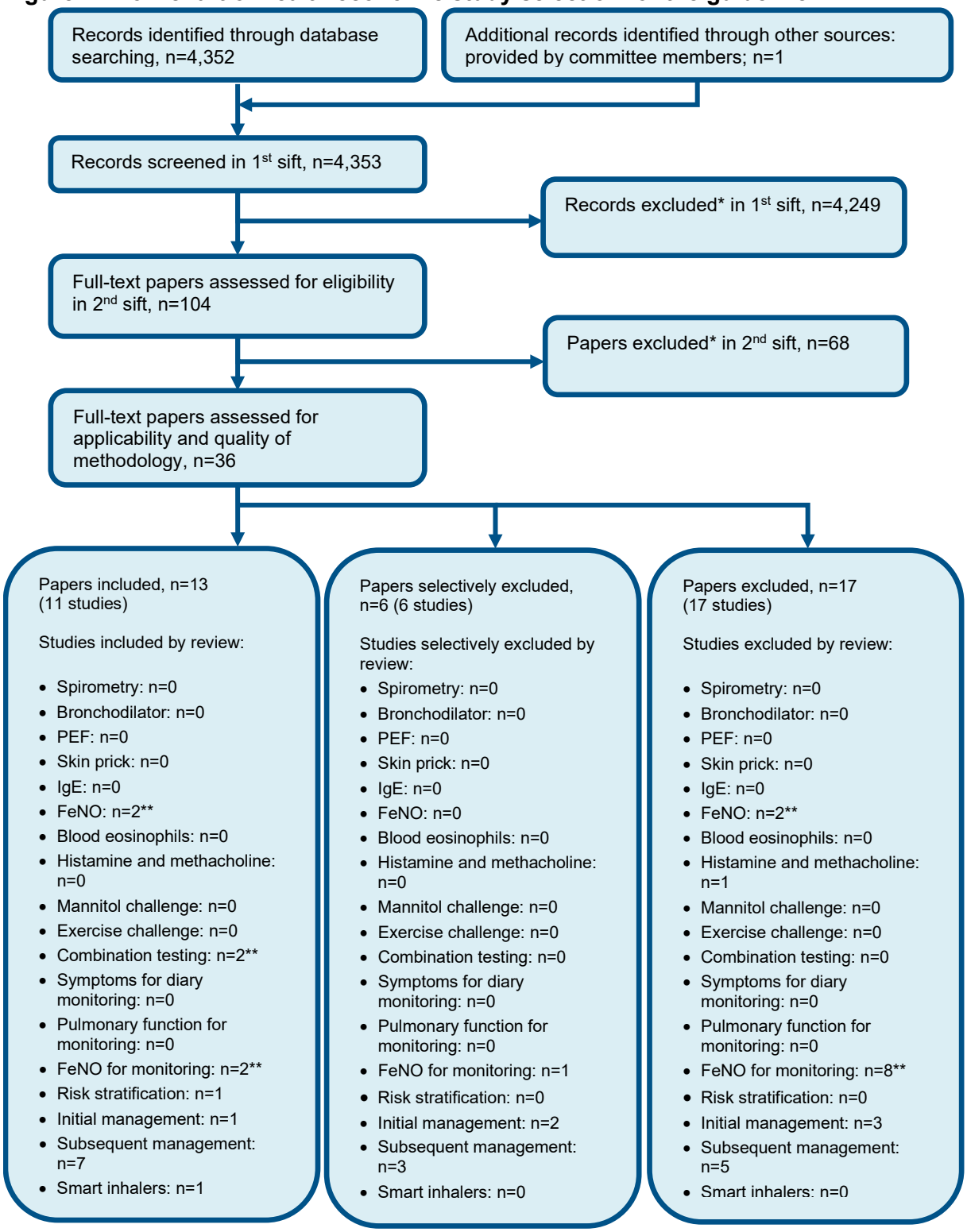
a. Downgraded by two increments due to concerns arising from the randomisation process and missing outcome data

b. Downgraded by two increments due to the 95%CI overlapping both MIDs (0.8-1.25)

c. Downgraded by two increments due to inadequate sample size (power <80%)

Appendix G – Economic evidence study selection

Figure 7: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
** Includes studies that are in multiple reviews

Appendix H Economic evidence tables

<table>
<tr><th>Study</th><th colspan="4">Lenney (2013)(Lenney et al., 2013)</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis:
CUA (health outcome: QALYs)

Study design: Within trial analysis based on MASCOT RCT(Lenney et al., 2013)
Approach to analysis:
Analysis of individual level resource use, with unit costs applied. Quality of life data collected for all patients via PAQLQ(S) questionnaire, with results directly transformed to QALYs. This was done by using an indexed PAQLQ(S) score to proxy for QALYs using a transformation (PAQLQ–1)/6, which generates a score within the range (0,1).QALYS calculated by under the</td>
<td>Population:
Patients aged 6–14 years, 11 months, with physician diagnosed asthma requiring frequent (7+ puffs) short-acting beta-2 agonist relief, with symptoms of asthma resulting in nocturnal wakening and/or asthma that has interfered with usual activities and/or exacerbations of asthma.

Cohort settings:
Mean age: 10.39 (SD = 2.17)
Male: 63.5%

Intervention 1:
Regular low-dose ICS - Inhaled fluticasone (ICS) propionate 100µg twice daily plus placebo tablet once daily</td>
<td>Total costs (mean per patient):
Intervention 1: £145
Intervention 2: £459
Intervention 3: £448
Incremental (2−1): £314.05
(95% CI: NR; p=0.48

Incremental (3−1): £303.24
(95% CI: NR; p=0.35)

Incremental (3-2); saves £10.81
(95% CI: NR; p=0.19)

Currency & cost year:
2009-2010 UK Pounds[b]

Cost components incorporated:
All relevant healthcare costs included, such as prescribed inhalers and</td>
<td>QALYs (mean per patient):
Intervention 1: 0.09
Intervention 2: 0.12
Intervention 3: 0.13
Incremental (2−1): 0.03
(95% CI: NR; p=0.46

Incremental (3−1): 0.04
(95% CI: NR; p=0.43)

Incremental (3-2); 0.02
(95% CI: NR; p=0.89)</td>
<td>Full incremental analysis (pa)[c]

<table>
<tr><th>Int</th><th>Cost</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th><th>% most CE at £30K:</th></tr>
<tr><td>1</td><td>£145</td><td>0.09</td><td colspan="3">Baseline</td><td>0%</td></tr>
<tr><td>2</td><td>£459</td><td>0.12</td><td colspan="3">Dominated by 3</td><td>60%</td></tr>
<tr><td>3</td><td>£448</td><td>0.13</td><td>£303.24</td><td>0.043</td><td>£6827</td><td>80%</td></tr>
</table>

ICS low dose plus regular montelukast is cost-effective at 20k cost per QALY. The PSA showed that it is also the most likely cost-effective strategy at £30,000 per QALY

Analysis of uncertainty:
• Bootstrapping
• Missing data handled by using different imputation assumptions informed by data collected on reasons for missing data.</td>
</tr>
</table>

curve approach and unadjusted patient-specific changes in QALYs. **Perspective:** UK NHS **Follow-up**: 48 weeks **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: n/a ; Outcomes: n/a	**Intervention 2:** Regular low dose ICS/LABA combination - Inhaled fluticasone propionate 100µg (ICS) and salmeterol (LABA) 50µg twice daily (combination inhaler) plus placebo tablet once daily **Intervention 3:** Regular low-dose ICS plus regular montelukast - Inhaled fluticasone propionate 100µg (ICS) twice daily plus montelukast 5-mg (LTRA) tablet once daily	prescribed medicine cost, over the counter medicine cost, GP costs, walk-in costs, specialist doctor cost, A&E visit costs and hospital admission costs.		
Data sources				
Health outcomes: Baseline events and effectiveness data sourced from based on the study RCT (Lenney, 2013). Resource use for 12 months reported by participants or carers for this within trial analysis. **Quality-of-life weights:** PAQLQ(S) transformed directly into QALY using an indexed PAQLQ(S) score to proxy for QALYs using a transformation (PAQLQ–1)/6. **Cost sources:** NHS Reference costs, BNF costs, Tesco pharmacy OTC medicine costs and PSSRU costs.				
Comments				
Source of funding: NIHR support through the MRCN and funding supplied from the HTA programme. **Limitations:** The trial enrolled children older than 12 which makes it not fully aligned with the protocol (5 – 12). The study suffered from high attrition and only a limited number of participants could be successfully randomised. Short time horizon may not adequately reflect long term outcomes and effects. unclear if utility weights were derived from PAQLQ(s)n using the preference of the UK general population. Treatment effects and outcomes based on the singular study RCT, may not reflect full scope of evidence. Patient diary used as sole source of resource use, this is prone to recall bias, and potential conflict of interest. **Other:**				
Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations				

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial, MASCOT = Management of Asthma in School age Children On Therapy, CUA = Cost-utility analysis, PAQLQ(S) = Standardised Paediatric Asthma Quality of Life Questionnaire (PAQLQ(S)), OTC = Over the counter, BNF

= British National Formulary, PSSRU = Personal Social Services Research Unit, NIHR = National Institute for Health and Care Research, MRCN = NIHR Medicines for Children Research Network, HTA = Health Technology Assessment. ICS = Inhaled corticosteroid, LABA = Long-acting beta2 agonist, LTRA = Leukotriene receptor antagonist.
(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
(b) 2009-2010 UK pounds
(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Price 2011(Price et al., 2011)/Wison 2010(Wilson et al., 2010)**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALY) **Study design:** Within-trial analysis (ELEVATE RCT) (Price et al., 2011) **Approach to analysis:** Analysis of individual level EQ-5D and resource use, with unit costs applied. QALYs calculated using area under the curve method. **Perspective:** UK NHS **Follow-up:** 2 years **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** Patients aged 12-80 years with diagnosed asthma who had received inhaled steroid for at least the last 12 weeks and had not received a long-acting β2-agonist or leukotriene antagonist in the previous 12 weeks. **Cohort settings:** Start age: 50 Male: 37.7% **Intervention 1 (n=181):** Moderate dose ICS/LABA (ICS = beclomethasone dipropionate, budesonide or fluticasone propionate, LABA = salmeterol or formoterol	**Total NHS costs (mean per patient):** Intervention 1: £869 Intervention 2: £956 Incremental (2−1): £88 (95% CI: NR; p=NR) Adjusted incremental[(b)]: £113 (95% CI:NR; p=NR) **Currency & cost year:** 2005 UK pounds **Cost components incorporated:** Prescribed medication and devices, primary and secondary care activity, lost productivity (not reported here)	**QALYs (mean per patient):** Intervention 1: 1.548 Intervention 2: 1.601 Incremental (2−1): 0.053 (95% CI:NR; p=NR) Adjusted incremental[(b)]: 0.009 (95% CI:NR; p=NR) **MiniAQLQ (mean per patient):** Intervention 1: 5.416 Intervention 2: 5.452 Incremental (2−1): 0.037 (95% CI:NR; p=NR) Adjusted incremental[(b)]: 0.034 (95% CI:NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £11,919 per QALY gained (using imputed data and adjusted for baseline utility) Probability ICS+LTRA cost effective (£20K/£30K threshold): 50%/53% **Analysis of uncertainty:** Results presented with complete cases only and analyses with imputed data with and without adjustments for baseline differences in QoL. No change to cost effectiveness conclusion.

	Fixed dose ICS/LABA combination inhaler available: Seretide or Symbicort) **Intervention 2 (n=169):** Moderate dose ICS + LTRA (ICS = beclometasone dipropionate, budesonide or fluticasone propionate, LTRA = montelukast 10 mg, once daily or zafirlukast 20 mg, twice daily Inhaled short-acting β2-agonist was permitted throughout the study 'as needed' in both arms.			
Data sources				
Health outcomes: Within study participant completed questionnaires at baseline and each study visit over 2 years. **Quality-of-life weights:** Within-RCT analysis: EQ-5D UK tariff. **Cost sources:** Resource use from primary care practice databases using MIQUEST (www.connectingforhealth.nhs.uk/miquest), APOLLO SQL SUITE (www.apollo-medical.com/products/sql.htm) and manual extraction from practices. Unit costs from NHS reference costs, PSSRU and ePACT.				
Comments				
Source of funding: NIHR Health Technology Assessment programme. **Limitations:** Not all comparators from protocol included (no MART) and it is step up from low dose ICS + SABA rather than ICS+LABA. Montelukast or zafirlukast used in study. 2005 NHS unit costs may not reflect current NHS costs. Montelukast patent ended in 2012 allowing generics and reducing the market prices since the date of analysis. Montelukast out of patent reduces the price significantly since date of study. This would increase the cost-effectiveness of ICS+LTRA and possibly see it as cost-saving compared to ICS+LABA and therefore dominant for cost-effectiveness. This is one of 2 RCTs comparing ICS+LABA to ICTS+LTRA and therefore may not reflect the full body on clinical evidence. The pragmatic nature of the RCT on which the evaluation is based may not reflect the true treatment effect sizes. **Other:**				

Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; ePACT: Electronic Prescribing Analysis and CosT; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Including imputed data and adjusted for baseline values

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitation

Study	**NICE 2017 (NG80)(National Institute for Health and Care Excellence, 2017)**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision analytic model **Approach to analysis:** Markov structure with four states: baseline treatment (starting health state), stepped up treatment, switched treatment and death.[a] Cycle length = 1-month cycle length. **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration:**[b] n/a **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** Adults over 16 years of age, whose asthma has remained uncontrolled using routine low dose inhaled corticosteroids (ICSs) and short acting beta agonists (SABAs) for symptom relief. **Cohort settings:** Start age: 44 years Male: 40% **Intervention 1:** Low dose ICS **Intervention 2:** Low dose ICS/LABA	**Total costs (mean per patient):** See cost effectiveness column for full incremental analysis. **Currency & cost year:** 2016 UK pounds **Cost components incorporated:** Drug costs and healthcare utilisation (including exacerbation and non-exacerbation HC use)	**QALYs (mean per patient):** See cost effectiveness column for full incremental analysis.	**Full incremental analysis**[c]: Int. / QALYs / Costs / ICER / Probability CE @£20K ICS+ LTRA / 16.222 / £3,923 / - / 71% Moderate ICS / 16.221 / £4,653 / Dominated / 13% ICS/LABA / 16.234 / £4,639 / £56,977 / 12% Low dose ICS / 16.113 / £5,068 / Dominated / 3% A number of sensitivity analyses conducted, none changed conclusion of base case, ICS+LTRA remained cost effective option. These included: - using cheapest medication brands - doubling and halving length of exacerbations - decreasing disutility associated with exacerbations

	Intervention 3: Low dose ICS + LTRA **Intervention 4:** Moderate ICS dose All of the strategies included assume the use of SABAs for short-term symptom relief.			- 10-year horizon - assume no treatment switch for low/moderate dose ICS - assume equal treatment switching - adherence - hospitalisation rate for low dose ICS - 1.5% discount rate - Change exacerbation rate ratio / use upper confidence interval - increase number of GP appointments for those starting on LTRA - increase disutility for those starting on ICS+LTRA - reduce cost of ICS/LABA
Data sources				
Health outcomes: RCTs identified in systematic review of clinical evidence undertaken as part of NG80 guideline used to identify baseline and treatment effect estimates. Low dose ICS+LABA used as baseline with yearly exacerbation and hospitalisation rates taken from Price 2011. Rate ratios for low dose ICS+LTRA (Bjermer 2003 for exacerbations and Price 2011 for hospitalisations); low dose ICS (O'Byrne 2001 for both exacerbations and hospitalisations); moderate dose ICS (Greening 1994 for exacerbations, assumption for hospitalisations). SABA use difference versus low dose ICS+LABA: low dose ICS+LTRA (Ilowite 2004); low dose ICS (O'Byrne 2001), moderate dose (Greening 1994). Adherence and treatment switching (Price 2011 and assumption). All-cause mortality national life tables, asthma related mortality (DeVries 2010). **Quality-of-life weights:** Baseline utility and decrement for starting on low dose ICS+LTRA taken from Price 2011 (EQ-5D UK tariff), utility decrement for hospitalised and non-hospitalised exacerbation taken from Lloyd 2007 (EQ-5D UK tariff). Duration of exacerbation expert opinion. **Cost sources:** Drug Tariff, BNF, PCA, NHS reference costs, PSSRU and expert opinion. Cost of drugs based on proportion of prescriptions, for LTRA, 97% of prescriptions were montelukast.				
Comments				
Source of funding: NICE. **Limitations:** Comparators not directly relevant to review question. Not all comparators from protocol included (no MART) and it is step up from low dose ICS + SABA rather than ICS/LABA. 2016 NHS unit costs may not reflect current NHS costs. Direct evidence only existed against ICS/LABA, no direct evidence between low dose ICS, moderate dose ICS and ICS + LTRA. Most of the RCT evidence used in model is not included in clinical review due to incorrect intervention/comparator/study population or outcomes that are not extractable (Bjermer 2003, Greening 1994 and O'Byrne 2001). Heavy reliance on a single pragmatic RCT (Price 2011) for several inputs including baseline exacerbation rate for ICS/LABA, disutility of starting on low dose ICS+LTRA, resource use, drug adherence and switching. Price 2011 categorised as low dose ICS/LABA and low dose ICS+LTRA in this model, despite mean ICS dose of 425-450µg. Model assumptions biased against ICS+LTRA. Disutility for exacerbating based on single study and considered high. Non-exacerbation-related healthcare costs remained high for ICS+LTRA throughout the model. **Other:**				

Overall applicability:[d] Partially applicable **Overall quality:**[e] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; ICS= inhaled corticosteroids; LABA= long acting beta agonists; LTRA= leukotriene receptor antagonists; NR= not reported; pa= probabilistic analysis; PCA = prescription cost analysis; QALY= quality-adjusted life years; RCT= randomised controlled trial; SABA= short acting beta agonists.

(a) If the individual does not respond to treatment, then they either switch to another second-line preventer or they have an additional second-line preventer added onto their current therapy. In the model if the individual starts on low dose ICS+LTRA then they can either have LABA replace the LTRA (switch) or have a LABA added onto their therapy (step-up). An assumption was made that if the individual starts on a single ICS inhaler then if their asthma remains uncontrolled they will always have an additional preventer added (step-up) as opposed to having their ICS inhaler replaced (switch). This is in line with best practice.

(b) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(c) Estimates are ranked from the least costly to the most costly. Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Wickstrom 2009(Wickstrom et al., 2009)**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (Health outcome: severe exacerbation) **Study design:** Within trial analyses (multiple papers). **Approach to analysis:** Systematic review that conducts 5 separate economic evaluations, based on 5 separate RCTs. Attaching Danish unit costs to resource	**Population:** Adults and children over 8 years of age with persistent asthma. **Cohort settings:** Mean age: 36-45 Male: n/a **Interventions:** First treatment change:	**Total costs (mean per patient):** First treatment change: Rabe 2006: 1) £437 2) £445 Incremental (2−1): £8 O'Byrne 2005: 1) £370 2) £351 Incremental (2−1): saves £19	**No. severe exacerbations (events per patient per year):** First treatment change: Rabe 2006: 1) 0.29 2) 0.19 Incremental (2−1): 0.10 fewer O'Byrne 2005: 1) 0.40 2) 0.19	**ICER (Intervention 2 versus Intervention 1):** Rabe 2006: Intervention 2 costs an additional £82 per exacerbation avoided. Kuna 2007 Intervention 2 dominated intervention 1 by reducing exacerbations and reducing costs to the health service. Bousquet 2007 Intervention 2 costs an additional £868 per

use parameters. For trials with less than 1 year duration (24 or 26 weeks), effects and resource use were extrapolated to 1 year. **Perspective:** Danish Healthcare perspective **Follow-up:** 1 year **Treatment effect duration:**[a] 1 year **Discounting:** N/A	Rabe 2006: 1. ICS/LABA (low dose) 2. MART (ICS/LABA low dose) O'Byrne 2005: 1. ICS/LABA (low dose) 2. MART (ICS/LABA low dose) Subsequent treatment change Kuna 2007:[b] 1. ICS/LABA (moderate dose) 2. MART (ICS/ LABA, low dose) Bousquet 2007: 1. ICS/LABA (high dose) 2. MART (ICS/LABA, moderate dose) O'Byrne 2005: 1. ICS (moderate dose) 2. MART (ICS/LABA, low dose) Vogelmeir 2005: 1. ICS/LABA (high dose	Subsequent treatment change: Kuna 2007 1) £631/£636 2) £447 Incremental (2−1): saves £184/£188 Bousquet 2007 1) £594 2) £650 Incremental (2−1): £56 O'Byrne 2005 1) £362 2) £351 Incremental (2−1): saves £12 Vogelmeir 2005 1) £510 2) £528 Incremental (2-1): £18 **Currency & cost year:** Danish Krone presented here as 2007 UK GBP[c]	Incremental (2−1): 0.21 fewer Subsequent treatment: change Kuna 2007 1) 0.32/0.38 2) 0.24 Incremental (2−1): 0.08/0.14 fewer (p=0.0048/p<0.001) Bousquet 2007 1) 0.31 2) 0.25 Incremental (2−1): 0.06 fewer (p=0.039) O'Byrne 2005 1) 0.35 2) 0.19 Incremental (2−1): 0.16 fewer (p<0.001) Vogelmeir 2005 1) 0.23 2) 0.19 Incremental (2−1): 0.04 fewer (p=0.023)	exacerbation avoided. O'Byrne 2005 (both analyses) Intervention 2 dominated intervention 1 by reducing exacerbations and reducing costs to the health service. Vogelmeir 2005 Intervention 2 costs an additional £458 per exacerbation avoided. Sensitivity analyses conducted: - Medication costs reduced to the lowest priced. - Unit costs of hospitalisation changed to different costs between ICU, general ward. - Unit costs for specialist and GP made to be equal. None of these univariate analyses changed the results of the base case analysis.

	2. MART (ICS/LABA, moderate dose) All intervention 1 had SABA as a reliever to be used as needed.	**Cost components incorporated:** Asthma medication Hospitalisation Unplanned emergency visit Visit to GP Visit to pulmonologist.		
Data sources				
Health outcomes: Number of severe exacerbations experienced, taken from within trials: Rabe 2006, Kuna 2007; Bousquet 2007; O'Byrne 2005; Vogelmeir 2005.(Bousquet et al., 2007, Kuna et al., 2007, O'Byrne et al., 2005, Rabe et al., 2006, Vogelmeier et al., 2005) **Quality-of-life weights:** N/A **Cost sources:** Resource use taken from within each trial. Danish national unit costs applied.				
Comments				
Source of funding: Astra Zeneca **Limitations:** Resource use for each trial was pooled across multiple countries rather than just the UK. In addition, Danish unit costs were applied, making the results less applicable to UK NHS perspective. EQ-5D not included as an outcome, though reported outcomes would suggest it is at least not lower in the MART group. Time horizon of only 1 year may not be capturing the full effect of interventions. Limited sensitivity analyses conducted. Unit costs from 2007, may not reflect current NHS costs. Rabe 2006 and O'Byrne 2005 are indirect evidence for first treatment change as all participants had received moderate dose ICS prior to trial entry. Potential conflict of interest. **Other:**				
Overall applicability:[d] Partially applicable **Overall quality:**[e] Potentially serious limitations				

Abbreviations: CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years, ICS: inhaled corticosteroids; LABA; long-acting beta-agonist; MART: maintenance and reliever therapy

a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
b) There were two ICS/LABA arms compared to MART. One with budesonide/formoterol and the other with salmetorol/fluticasone. Both presented here.
c) Converted using 2007 purchasing power parities.
d) Directly applicable / Partially applicable / Not applicable
e) Minor limitations / Potentially serious limitations / Very serious limitations

<table>
<tr><th>Study</th><th colspan="4">Mangia (2021)(Mangia et al., 2021)</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis:
CUA (health outcome: QALY)

Study design:
Decision analytical model

Approach to analysis:
Markov model based on - Two phase III studies, ARGON and IRIDIUM, investigated the effectiveness and safety of Enerzair Breezhaler.

Using a Markov model with two mutually exclusive health states (daily symptoms and "death") across a lifetime horizon (50 years), the clinical experience of asthma patients is replicated at the cohort level until the cohort of patients passes away completely. To reflect the average length of an asthmatic exacerbation,</td>
<td>Population:
Adult patients with asthma aged 18 years and older who are inadequately controlled despite treatment with high-dose inhaled corticosteroids and LABAs.

Cohort settings:
Start age: 52-53
Male: 37-38%

Intervention 1:
ICS/LABA/LAMA: Indacaterol/ glycopyrronium/ Mometasone furoate 150/50/320 µg once daily.

Intervention 2:
ICS/LABA: Mometasone/ Indacaterol 150/320 µg, once daily</td>
<td>Total costs (mean per patient):
Intervention 1: NR
Intervention 2: NR
Intervention 3: NR
Intervention 4: NR

Incremental (1−2): £4,919
(95% CI: NR; p=NR)

Incremental (1−3): £2,641
(95% CI: NR; p=NR)

Incremental (1−4): saves £3,331
(95% CI: NR; p=NR)

Currency & cost year:
2021 Euros (presented here as 2021 UK pounds[(b)])
Cost components incorporated:</td>
<td>QALYs (mean per patient):
Intervention 1: NR
Intervention 2: NR
Intervention 3: NR
Intervention 4: NR

Incremental (1−2): 0.34
(95% CI: NR; p=NR)

Incremental (1−3): 0.21 (95% CI: NR; p=NR)

Incremental (1−4): 0.25
(95% CI: NR; p=NR)</td>
<td>Pairwise comparisons:

<table>
<tr><th>Pairwise comparison</th><th>Inc QALY</th><th>Inc costs £</th><th>ICER £/QALY</th><th>% most CE at £19.7K:</th></tr>
<tr><td>1 vs 2</td><td>0.34</td><td>£4919</td><td>£14,601</td><td>65%</td></tr>
<tr><td>1 vs 3</td><td>0.21</td><td>£2641</td><td>£12,331</td><td>80%</td></tr>
<tr><td>1 vs 4</td><td>0.25</td><td>Saves £3331</td><td>Dominates</td><td>100%</td></tr>
</table>

Intervention 1 when compared to intervention 2,3 or 4 is expected to be more effective and either cost saving or with an ICER well below conventional willingness-to-pay threshold.

In addition, Intervention 4 is dominated by intervention 3 (less costly and more effective) and is not cost effective compared to intervention 2 (ICER >30K).

Analysis of uncertainty:
Bootstrapping included. Missing data handled by using different imputation assumptions informed by data collected on reasons for missing data.</td>
</tr>
</table>

the simulated time is divided into equal cycles of 4 weeks. **Perspective:** Italian Healthcare perspective **Time horizon:** lifetime **Discounting:** Costs:; 3% Outcomes: 3%	**Intervention 3:** ICS/LABA: Salmeterol/Fluticasone 50/500 µg, twice daily **Intervention 4:** ICS/LABA plus LAMA: Salmeterol/fluticasone 50/500 µg, twice daily plus tiotropium 5 µg once daily	Pharmaceutical costs and exacerbation management costs		
Data sources				
Health outcomes: Effectiveness data taken from Two phase III studies, ARGON and IRIDIUM, investigated the effectiveness and safety of Enerzair Breezhaler. **Quality-of-life weights:** Reported to be EQ-5D derived from clinical trial although the trial does not seem to have included an EQ-5D questionnaire. **Cost sources:** Resource use costs sourced from Italian health sources such as DRG 97/98, price of medicines derived from the ex-factory price after mandatory discounts the ministry of health in addition to studies looking at the costs of Asthma in Italy (Negro (2016).				
Comments				
Source of funding: Novartis Farma, Italy. **Limitations:** Italian healthcare perspective, uses 3% discounted not 3.5%, also lack of clarity in where exactly QALYs are derived. Source of outcome data taken from only two clinical trials, may not reflect full scope of evidence. Baseline source of outcome unclear, sources of costs derived from Italian healthcare sources which may not be applicable to the NHS. Potential conflict of interest. **Other:**				
Overall applicability:[c] Partially applicable		**Overall quality:**[d] Potentially serious limitations		

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years. LAMA = Long-acting muscarinic antagonists, LABA = Long-acting beta-2 agonist, ICS = Inhaled corticosteroids, IND = indacaterol, acetate GLY= Glycopyrronium bromide, MF = Mometasone furoate, SAL = Salmeterol, FLU = Fluticasone, TIO= Tiotropium.

(a) Converted using 2021 purchasing power parities(Organisation for Economic Co-operation and Development (OECD), 2012)

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

<table>
<tr><th>Study</th><th colspan="4">Mtibaa (2021)(Mtibaa et al., 2021)</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis:
CUA (health outcome: QALY)

Study design:
Decision analytical model

Approach to analysis:
Markov model using effectiveness data from two phase III studies, ARGON and IRIDIUM. Three major health states:
• day-to-day symptoms without exacerbations
• day-to-day symptoms with exacerbations,
• death.
Patients started in the “day-to-day asthma symptoms without exacerbations” state, which captured the day-to-day quality of life associated with high-dose IND/GLY/MF</td>
<td>Population:
Patients (aged ≥18 years) with a diagnosis of moderate-to-severe asthma not adequately controlled by a maintenance combination of a LABA and a moderate- or high-dose ICS.

Cohort settings:
Start age: NR
Male: NR

Intervention 1:
LABA/LAMA/ICS (IND/ GLY/MF) Once daily 150/50/160 µg

Intervention 2:
LABA/ICS: SAL/FLU 50/500 µg Twice daily (IRIDIUM RCT)

Intervention 3:
LABA/ICS (SAL/FLU; 50/500 µg, twice</td>
<td>Total costs:

IRIDIUM Trial
Intervention 1: £18,477
Intervention 2: £20,230
Incremental (1−2): saves £1753.
(95% CI: NR; p=NR)

ARAGON TRIAL
Intervention 1: £18,529
Intervention 3: £28,156
Incremental (1−3): saves £9627.
(95% CI: NR; p=NR)

Currency & cost year:
2020 Canadian dollars (presented here as 2020 UK pounds[(b)])</td>
<td>Total QALYs

IRIDIUM
Intervention 1: 19.33
Intervention 2: 19.04
Incremental (1−2): 0.29
(95% CI: NR; p=NR)

ARAGON
Intervention 1: 18.37
Intervention 3: 18.06
Incremental (1−3): 0.31
(95% CI: NR; p=NR)</td>
<td>Full incremental analysis (pa)

<table>
<tr><th>Intervention</th><th>Inc QALY</th><th>Inc costs £</th><th>ICER £/QALY</th></tr>
<tr><td>1</td><td colspan="3">Reference</td></tr>
<tr><td>2</td><td>0.29</td><td>Saves £1753</td><td>Dominated</td></tr>
<tr><td>3</td><td>0.31</td><td>Saves £9627</td><td>Dominated</td></tr>
</table>

Intervention 1 dominated intervention 2 and intervention 3(more effective and less costly).

Probability intervention 1 cost effective versus intervention 3 (£20K threshold): ~90%
Probability intervention 1 cost effective versus intervention 2 (£20K threshold): ~40%
40%

Analysis of uncertainty:
Scenario analysis between intervention 1 and intervention 3. Results found did not change the conclusion of the base-case scenario.

<table>
<tr><th>Scenario</th><th>Inc TC</th><th>Inc QALYs</th><th>Conclusion</th></tr>
<tr><td>3% discounting rate</td><td>Saves £2675</td><td>0.21</td><td>Intervention 1 dominates 3</td></tr>
</table>
</td>
</tr>
</table>

compared with the comparator treatments. Cycle duration 4 weeks. **Perspective:** Canadian Healthcare perspective **Time horizon:** lifetime **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: 1.5%; Outcomes: 1.5%	daily) + LAMA (TIO; 5 µg, once daily) (ARAGON RCT)	**Cost components incorporated:** Drug costs, Healthcare resource use per exacerbation		10-year time horizon	Saves £3879	0.12	Intervention 1 dominates 3
				Inclusion of discontinuation in model	Saves £9621	0.32	Intervention 1 dominates 3
Data sources							
Health outcomes: Effectiveness data taken from two phase III studies, ARGON and IRIDIUM, which investigated the effectiveness and safety of high dose ICS/LABA/- + LAMA against ICS/LABA/LAMA. **Quality-of-life weights:** Sourced from ARGON and IRIDIUM RCTs where AQLQ results were subsequently mapped to EQ-5D using algorithm from Sheffield Health Economics group. **Cost sources:** Unit costs derived from Ontario case costing, with drug costs sourced from Ontario drug benefits formulary.							
Comments							
Source of funding: Novartis Farma AG. **Limitations:** Canadian healthcare perspective. Uses 1.5% discounted not 3.5%. AQLQ mapped to EQ-5D for quality of life data. Source of outcome data taken from only two clinical trials, may not reflect full scope of evidence. Costs sourced from Canadian health sources which may not be applicable to NHS. Potential conflict of interest. **Other:**							
Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations							

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years. LAMA = Long-acting muscarinic antagonists, LABA = Long-acting beta-2 agonist, ICS = Inhaled corticosteroids, IND = indacaterol, acetate GLY= Glycopyrronium bromide, MF = Mometasone furoate, SAL = Salmeterol, FLU = Fluticasone, TIO= Tiotropium.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2020 purchasing power parities(Organisation for Economic Co-operation and Development (OECD), 2012)

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Health economic model

The health economic model is detailed in the economic report.

Appendix J – Excluded studies

Clinical studies

Table 19: Studies excluded from the clinical review

Study	Code [Reason]
Aalbers, Rene (2010) Fixed or adjustable maintenance-dose budesonide/formoterol compared with fixed maintenance-dose salmeterol/fluticasone propionate in asthma patients aged >or=16 years: post hoc analysis of a randomized, double-blind/open-label extension, parallel-group study. Clinical drug investigation 30(7): 439-51	- Comparator in study does not match that specified in this review protocol *Study compared dosing regimens of different ICS/LABA combinations - not a relevant comparison for this review*
Abbas, A, Maheshwari, MP, Siddiqui, ZA et al. (2016) Role of long acting β2 agonist salmeterol, in management of mild to moderate asthmatic patients. Pakistan journal of medical and health sciences 10(4): 1112-1115	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Adams, N P, Bestall, J C, Jones, P W et al. (2005) Inhaled fluticasone at different doses for chronic asthma in adults and children. The Cochrane database of systematic reviews: cd003534	- Study does not contain an intervention relevant to this review protocol
Adams, N.; Bestall, J.; Jones, P. (2001) Inhaled beclomethasone at different doses for long-term asthma. Cochrane database of systematic reviews (Online): cd002879	- Study does not contain an intervention relevant to this review protocol
Adams, N; Bestall, J M; Jones, P W (2002) Inhaled fluticasone at different doses for chronic asthma. The Cochrane database of systematic reviews: cd003534	- Study does not contain an intervention relevant to this review protocol
Adams, N; Bestall, J; Jones, P (2001) Beclomethasone at different doses for chronic asthma (review). The Cochrane database of systematic reviews: cd002879	- Duplicate reference
Adams, Nick P, Bestall, Janine C, Jones, Paul et al. (2008) Fluticasone at different doses for chronic asthma in adults and children. The Cochrane database of systematic reviews: cd003534	- Study does not contain an intervention relevant to this review protocol
Adams, NP; Bestall, JC; Jones, P (2000) Budesonide at different doses for chronic asthma. Cochrane Database of Systematic Reviews	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
Affrime, M B, Kosoglou, T, Thonoor, C M et al. (2000) Mometasone furoate has minimal effects on the hypothalamic-pituitary-adrenal axis when delivered at high doses. Chest 118(6): 1538-46	- Comparator in study does not match that specified in this review protocol *Study compared different dosing regimens of ICS - not relevant to this review*
Agarwal, R, Khan, A, Aggarwal, A N et al. (2009) Is the SMART approach better than other treatment approaches for prevention of asthma exacerbations? A meta-analysis. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace 71(4): 161-9	- No additional studies identified through reference checking
Agusti, Alvar, Fabbri, Leonardo, Lahousse, Lies et al. (2022) Single inhaler triple therapy (SITT) in asthma: Systematic review and practice implications. Allergy 77(4): 1105-1113	- No additional studies identified through reference checking
Aisanov, Zaurbek, Avdeev, Sergey, Arkhipov, Vladimir et al. (2022) SYmbicort given as needed in mild asthma (SYGMA study): a retrospective subanalysis of the Russian population. The Journal of asthma : official journal of the Association for the Care of Asthma 59(5): 989-997	- Study does not contain an intervention relevant to this review protocol *BUD/FORM as needed, not regular as specified in review protocol*
Akpinarli, A, Tuncer, A, Saraclar, Y et al. (1999) Effect of formoterol on clinical parameters and lung functions in patients with bronchial asthma: a randomised controlled trial. Archives of disease in childhood 81(1): 45-8	- Study does not contain an intervention relevant to this review protocol *Formoterol used as sole therapy*
Albertson, Timothy E; Richards, John R; Zeki, Amir A (2016) The combination of fluticasone furoate and vilanterol trifenatate in the management of asthma: clinical trial evidence and experience. Therapeutic advances in respiratory disease 10(1): 43-56	- Review article but not a systematic review
Allison, D.E.; Kew, K.M.; Boyter, A.C. (2014) Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS for adults with asthma. Cochrane Database of Systematic Reviews 2014(11): cd011397	- No additional studies identified through reference checking
Anderson, Debbie E; Kew, Kayleigh M; Boyter, Anne C (2015) Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma. The Cochrane database of systematic reviews: cd011397	- Duplicate reference

Study	Code [Reason]
Anonymous (2010) Long-acting beta(2)-agonist and inhaled corticosteroid combination therapy for adult persistent asthma: systematic review of clinical outcomes and economic evaluation. CADTH technology overviews 1(3): e0120	- More recent systematic review included that covers the same topic
Anonymous (2007) Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. American journal of respiratory and critical care medicine 175(3): 235-42	- Comparator in study does not match that specified in this review protocol *Study compared ICS plus montelukast to continuing previous treatment plus placebo - not a relevant comparator in this review*
Anonymous. (2010) Three good options for step-up therapy for asthmatic children (BADGER). Journal of the National Medical Association 102(7): 661-662	- No additional studies identified through reference checking
Aubier, M, Pieters, W R, Schlosser, N J et al. (1999) Salmeterol/fluticasone propionate (50/500 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. Respiratory medicine 93(12): 876-84	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA combination inhaler to concurrent inhalation via two separate inhalers - not a relevant comparison for this review*
Axelsson, I., Naumburg, E., Prietsch, S.O.M. et al. (2019) Effects of inhaled corticosteroids on growth in children with persistent asthma: Impact of drug molecules and delivery devices - An overview of Cochrane reviews. Paediatric Respiratory Reviews 32: 28-29	- Review article but not a systematic review
Aziz, I; Wilson, A M; Lipworth, B J (2000) Effects of once-daily formoterol and budesonide given alone or in combination on surrogate inflammatory markers in asthmatic adults. Chest 118(4): 1049-58	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Bacharier, Leonard B, Raissy, Hengameh H, Wilson, Laura et al. (2004) Long-term effect of budesonide on hypothalamic-pituitary-adrenal axis function in children with mild to moderate asthma. Pediatrics 113(6): 1693-9	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Baggott, C, Hardy, J, Sparks, J et al. (2020) Self-titration of inhaled corticosteroid and β2-agonist in response to symptoms in mild asthma: a pre-specified analysis from the PRACTICAL randomised controlled trial. The european respiratory journal 56(4)	- Study does not contain an intervention relevant to this review protocol *ICS/formoterol as needed vs regular ICS/formoterol*

Study	Code [Reason]
Barbon, C.E.; Angeles, R.R.; Jorge, M.P.I. (2019) Efficacy and safety of as-needed corticosteroid plus formoterol monotherapy in adolescents and adults with mild and intermittent asthma: Meta analysis of randomised controlled trials. Respirology 24(supplement2): 201	- Conference abstract
Barbon, C.E. and Fernandez, L. (2020) Efficacy and safety of as-needed corticosteroid plus fast or short-acting beta-agonists monotherapy in patients with mild asthma: a meta-analysis of randomised controlled trials. European Respiratory Journal 56(supplement64)	- Conference abstract
Barnes, P J (2001) Clinical outcome of adding long-acting beta-agonists to inhaled corticosteroids. Respiratory medicine 95supplb: 12-6	- Review article but not a systematic review
Barnes, PJ, O'Byrne, PM, Rodriguez Roisin, R et al. (2000) Treatment of mild persisitent asthma with low doses of inhaled Budesonide alone or in combination with Formoterol. Thorax 55(suppl3): a4	- Study does not contain an intervention relevant to this review protocol *Study examined as-needed budesonide/formoterol - not relevant to this review*
Barthwal, MS and Meshram, S (2017) A randomized, double-blind study comparing the efficacy and safety of a combination of formoterol and ciclesonide with ciclesonide alone in asthma subjects with moderate-to-severe airflow limitation. Lung India 34(1): 111-112	- Not a peer-reviewed publication *Letter to editor*
Basu, K., Donald, H.P., Lipworth, B.J. et al. (2010) Better asthma control with montelukast than salmeterol in arg-16homozygous children with asthma. Thorax 65(suppl4): a154	- Conference abstract
Basu, K., Donald, H.P., Lipworth, B.J. et al. (2011) Comparison of montelukast versus salmeterol in children with asthma carrying at-risk beta2adrenergic receptor polymorphism: A genotype-stratified randomised controlled trial. Journal of Allergy and Clinical Immunology 127(2suppl1): ab212	- Conference abstract
Bateman, E D, Britton, M, Carrillo, J et al. (1998) Salmeterol/Fluticasone combination inhaler: a new, effective and well tolerated treatment for	- Comparator in study does not match that specified in this review protocol

Study	Code [Reason]
asthma. Clinical drug investigation 16(3): 193-201	*Study compared combination ICS/LABA to concurrent ICS + LABA - not a relevant comparison in this review*
Bateman, E., O'Byrne, P.M., FitzGerald, J.M. et al. (2019) Influence of prior treatment upon the efficacy of as-needed budesonide/formoterol in mild asthma in the sygma 1 and 2 studies. American Journal of Respiratory and Critical Care Medicine 199(9)	- Full text paper not available
Bateman, E, Pauwels, R, Boushey, H et al. (2004) Aiming for total control of asthma significantly improves asthma-related quality of life: salmeterol/fluticasone propionate versus fluticasone propionate alone. American journal of respiratory and critical care medicine 169(7): a87	- Duplicate reference
Bateman, ED, Bantje, TA, Joao Gomes, M et al. (2001) Budesonide/formoterol in a single inhaler improves asthma control more effectively than a higher dose of fluticasone. European respiratory journal 18(suppl33): 21s	- Conference abstract
Bateman, ED, Bantje, TA, Joao Gomes, M et al. (2001) Symbicort (Budesonide/eformoterol) turbohaler controls asthma more effectively than fluticasone diskus. Thorax 56(suppl3): iii63	- Conference abstract
Bateman, Eric D, Bantje, Theo A, Joao Gomes, Maria et al. (2003) Combination therapy with single inhaler budesonide/formoterol compared with high dose of fluticasone propionate alone in patients with moderate persistent asthma. American journal of respiratory medicine : drugs, devices, and other interventions 2(3): 275-81	- Comparator in study does not match that specified in this review protocol *Study compared moderate-dose ICS (500 mcg FP per day(to low-dose ICS/LABA (320/9 mcg BUD/FORM per day) - not a relevant comparator in this review*
Bateman, Eric D, Busse, William, Pedersen, Soren E et al. (2019) Global Initiative for Asthma 2016-derived asthma control with fluticasone propionate and salmeterol: A Gaining Optimal Asthma Control (GOAL) study reanalysis. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 123(1): 57-63e2	- Secondary publication of an included study that does not provide any additional relevant information
Bateman, Eric D, Harrison, Tim W, Quirce, Santiago et al. (2011) Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on	- Secondary publication of an included study that does not provide any additional relevant information

Study	Code [Reason]
different treatment steps. Respiratory research 12: 38	*Secondary analysis of primary studies included in this review*
Bateman, Eric, Nelson, Harold, Bousquet, Jean et al. (2008) Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. Annals of internal medicine 149(1): 33-42	- No additional studies identified through reference checking
Beasley, R., Patel, M., Pilcher, J. et al. (2013) Maintenance and reliever budesonide/formoterol therapy has a favourable risk/benefit profile in real-world asthma. Respirology 18(suppl2): 13	- Conference abstract
Beasley, Richard, Harrison, Tim, Peterson, Stefan et al. (2022) Evaluation of Budesonide-Formoterol for Maintenance and Reliever Therapy Among Patients With Poorly Controlled Asthma: A Systematic Review and Meta-analysis. JAMA network open 5(3): e220615	- No additional studies identified through reference checking
Beasley, Richard, Holliday, Mark, Reddel, Helen K et al. (2019) Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. The New England journal of medicine 380(21): 2020-2030	- Population not relevant to this review protocol *Participants were not receiving ICS at baseline*
Becker, Allan B, Kuznetsova, Olga, Vermeulen, J et al. (2006) Linear growth in prepubertal asthmatic children treated with montelukast, beclomethasone, or placebo: a 56-week randomized double-blind study. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 96(6): 800-7	- Population not relevant to this review protocol *Participants were not receiving ICS at baseline*
Beeh, Kai-Michael, Moroni-Zentgraf, Petra, Ablinger, Othmar et al. (2014) Tiotropium Respimat R in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma. Respiratory research 15: 61	- Inadequate study duration *Treatments given for 4 weeks - protocol specified minimum of 3 months for outcomes reported in this paper*
Befekadu, Elizabeth; Onofrei, Claudia; Colice, Gene L (2014) Tiotropium in asthma: a systematic review. Journal of asthma and allergy 7: 11-21	- No additional studies identified through reference checking
Berger, William E (2011) Mometasone furoate/formoterol in the treatment of persistent	- Review article but not a systematic review

Study	Code [Reason]
asthma. Expert review of respiratory medicine 5(6): 739-46	
Berger, William E, Ford, Linda B, Mahr, Todd et al. (2002) Efficacy and safety of fluticasone propionate 250 microg administered once daily in patients with persistent asthma treated with or without inhaled corticosteroids. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 89(4): 393-9	- Comparator in study does not match that specified in this review protocol *Study compared moderate-dose ICS to placebo - not a relevant comparison for this review*
Berger, William E and Noonan, Michael J (2010) Treatment of persistent asthma with Symbicort (budesonide/formoterol inhalation aerosol): an inhaled corticosteroid and long-acting beta2-adrenergic agonist in one pressurized metered-dose inhaler. The Journal of asthma : official journal of the Association for the Care of Asthma 47(4): 447-59	- Review article but not a systematic review
Bergmann, Karl-Christian, Lindemann, L, Braun, R et al. (2004) Salmeterol/fluticasone propionate (50/250 microg) combination is superior to double dose fluticasone (500 microg) for the treatment of symptomatic moderate asthma. Swiss medical weekly 134(34): 50-8	- Population not relevant to this review protocol *Participants had received treatments other than ICS or ICS/LABA before entering the study*
Bernstein, D.I., Bateman, E.D., Woodcock, A. et al. (2014) Efficacy and safety of once-daily fluticasone furoate/vilanterol (FF/VI) and FF over 12 weeks in patients with persistent asthma. American Journal of Respiratory and Critical Care Medicine 189(meetingabstracts)	- Conference abstract
Bernstein, J., Boner, A., Hamelmann, E. et al. (2014) Once-daily tiotropium respimat added-on to inhaled corticosteroids in a 1-year study in adolescent patients with symptomatic asthma is efficacious and well tolerated. Chest 146(4meetingabstract)	- Conference abstract
Bisgaard, H, Pedersen, S, Damkjaer Nielsen, M et al. (1991) Adrenal function in asthmatic children treated with inhaled budesonide. Acta paediatrica Scandinavica 80(2): 213-7	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Bisgaard, Hans, Hermansen, Mette Northman, Loland, Lotte et al. (2006) Intermittent inhaled corticosteroids in infants with episodic wheezing. The New England journal of medicine 354(19): 1998-2005	- Comparator in study does not match that specified in this review protocol *Study compared intermittent ICS plus SABA to placebo plus SABA - SABA alone is not an intervention listed in this review protocol*

Study	Code [Reason]
Bisgaard, Hans, Zielen, Stefen, Garcia-Garcia, Maria Luz et al. (2005) Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. American journal of respiratory and critical care medicine 171(4): 315-22	- Study not reported in English
Bjermer, Leif, Bisgaard, Hans, Bousquet, Jean et al. (2003) Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. BMJ (Clinical research ed.) 327(7420): 891	- Study does not contain an intervention relevant to this review protocol *Study compared low-dose ICS plus montelukast (100 mcg FP + 10 mg) to low-dose ICS/LABA (100 mcg FP + 50 mcg SAL twice daily) - low-dose ICS/LABA not relevant to this review protocol*
Blake, K V (1999) Montelukast: data from clinical trials in the management of asthma. The Annals of pharmacotherapy 33(12): 1299-314	- Review article but not a systematic review
Blake, K.V. and Raissy, H.H. (2018) Asthma Guidelines Priority Topic: Long-Acting Anti-Muscarinic Agents in Asthma Management as Add-On to Inhaled Corticosteroids. Pediatric, Allergy, Immunology, and Pulmonology 31(3): 199-203	- No additional studies identified through reference checking
Bleecker, E.R., Lotvall, J., O'Bryne, P.M. et al. (2012) Efficacy of fluticasone furoate (FF) as a monotherapy and in combination with vilanterol (VI) over 12 weeks in patients with persistent asthma. European Respiratory Journal 40(suppl56)	- Conference abstract
Bleecker, Eugene R, Bateman, Eric D, Busse, William W et al. (2012) Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 109(5): 353-358e4	- Comparator in study does not match that specified in this review protocol *Study compares ICS doses, not a relevant comparison in this review*
Bodzenta-Lukaszyk, A., Van Noord, J.A., Schroder-Babo, W.G. et al. (2011) Fluticasone propionate/formoterol fumarate combination therapy has comparable efficacy to its individual components administered concurrently. European Respiratory Journal 38(suppl55)	- Conference abstract
Bodzenta-Lukaszyk, Anna, Dymek, Andrzej, McAulay, Kirsten et al. (2011)	- Comparator in study does not match that specified in this review protocol

Study	Code [Reason]
Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study. BMC pulmonary medicine 11: 28	*Study compared two combinations of ICS/LABA (50/5 or 125/5 fluticasone/formoterol twice daily vs 50/25 or 125/25 mcg fluticasone/salmeterol twice daily) - within-drug class comparisons are not relevant to this review*
Bodzenta-Lukaszyk, Anna, Pulka, Grazyna, Dymek, Andrzej et al. (2011) Efficacy and safety of fluticasone and formoterol in a single pressurized metered dose inhaler. Respiratory medicine 105(5): 674-82	- Inadequate study duration *Study treated participants for 8 weeks - inadequate duration to assess the outcomes listed in this review protocol*
Bollmeier, Suzanne Gielow and Lee, Shin-Yu (2013) The emerging role of tiotropium for patients with asthma. The Annals of pharmacotherapy 47(5): 704-13	- No additional studies identified through reference checking
Boner, A, de Benedictis, F, La Rosa, M et al. (1999) Clincial Trial to compare the efficacy of two doses of fluticasone propionate (FP) 200 mcg/day and 400 mcg/day, administered for 6 weeks to asthmatic children, as assessed by bronchial responsiveness to methacholine. American journal of respiratory and critical care medicine 159(3pt2): a139	- Conference abstract
Botan, V., Miranda, M., Couto, S. et al. (2012) Influence of montelukast on the state of eosinophil activation in asthmatic children. World Allergy Organization Journal 5(suppl2): 81	- Conference abstract
Boulet, L.-P., Lee, L., Kerstjens, H. et al. (2020) CAPTAIN: Effects of age on response to triple therapy in patients with inadequately controlled asthma on ICS/LABA. European Respiratory Journal 56(supplement64)	- Conference abstract
Bouros, D, Bachlitzanakis, N, Kottakis, J et al. (1999) Formoterol and beclomethasone versus higher dose beclomethasone as maintenance therapy in adult asthma. The European respiratory journal 14(3): 627-32	- Inadequate study duration *Study of inadequate duration to assess reported outcomes*
Boushey, Homer A, Sorkness, Christine A, King, Tonya S et al. (2005) Daily versus as-needed corticosteroids for mild persistent asthma. The New England journal of medicine 352(15): 1519-28	- Study does not contain an intervention relevant to this review protocol *Study compared low-dose ICS (400 mcg budesonide per day) to LTRA (20 mg zafirlukast) and intermittent moderate-dose ICS (800 mcg budesonide when symptoms*

Study	Code [Reason]
	worsened) - none are relevant to this review protocol
Bousquet, J., Gibbs, M., Gul, N. et al. (2017) Asthma control using fluticasone propionate/salmeterol: GOAL study re-analysis using GINA 2016 guidelines. European Respiratory Journal 50(supplement61)	- Conference abstract
Bousquet, Jean, Barnes, Neil, Gibbs, Michael et al. (2017) Asthma control using fluticasone propionate/salmeterol in Asian and non-Asian populations: a post hoc analysis of the GOAL study. BMC pulmonary medicine 17(1): 75	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis of GOAL (Bateman 2004)*
Braido, F., Troise, C., Canonica, G.W. et al. (2010) Budesonide/formoterol maintenance and reliever therapy, comparison between two different maintenance doses and predictive factors for the choice of the most appropriate mantenance dose. European Annals of Allergy and Clinical Immunology 42(6): 228	- Conference abstract
Brown, R., Chipps, B.E., Tashkin, D.P. et al. (2014) Effects of long-term treatment with budesonide/formoterol (BUD/ FM) delivered by pressurized metered-dose inhaler (pMDI) on symptoms in african-american and caucasian patients with moderate to severe asthma with and without fixed airway obstruction (FAO). Journal of Allergy and Clinical Immunology 133(2suppl1): ab2	- Conference abstract
Brown, Randall W, O'Brien, Christopher D, Martin, Ubaldo J et al. (2012) Long-term safety and asthma control measures with a budesonide/formoterol pressurized metered-dose inhaler in African American asthmatic patients: a randomized controlled trial. The Journal of allergy and clinical immunology 130(2): 362-7e9	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Bruce, SA and Scherer, YK (2005) Maintenance and symptom relief with budesonide plus formoterol reduced severe asthma exacerbations. Evidence-based nursing 8(3): 78	- Conference abstract
Buchvald, Frederik and Bisgaard, Hans (2003) Comparisons of the complementary effect on exhaled nitric oxide of salmeterol vs montelukast in asthmatic children taking regular inhaled budesonide. Annals of allergy, asthma & immunology : official publication of the American	- Inadequate study duration *Study treated participants for 2 weeks per treatment - inadequate duration to assess the outcomes listed in this review protocol*

Study	Code [Reason]
College of Allergy, Asthma, & Immunology 91(3): 309-13	
Buhl, R, Creemers, J P H M, Vondra, V et al. (2003) Once-daily budesonide/formoterol in a single inhaler in adults with moderate persistent asthma. Respiratory medicine 97(4): 323-30	- Comparator in study does not match that specified in this review protocol *Study compared regular ICS/LABA to low-dose ICS (400 mcg budesonide per day) - low-dose ICS is not a relevant intervention in this review*
Buhl, R and Vogelmeier, C (2007) Budesonide/formoterol maintenance and reliever therapy: a new treatment approach for adult patients with asthma. Current medical research and opinion 23(8): 1867-78	- Review article but not a systematic review
Buhl, Roland, Kuna, Piotr, Peters, Matthew J et al. (2012) The effect of budesonide/formoterol maintenance and reliever therapy on the risk of severe asthma exacerbations following episodes of high reliever use: an exploratory analysis of two randomised, controlled studies with comparisons to standard therapy. Respiratory research 13: 59	- No relevant outcomes identified
Bumbacea, D.; Dymek, A.; Mansikka, H. (2010) Fluticasone propionate/formoterol fumarate combination therapy has an efficacy and safety profile similar to that of its individual components administered concurrently: A randomised controlled trial. Thorax 65(suppl4): a83	- Conference abstract
Busse, W W, Bateman, E D, O'Byrne, P M et al. (2014) Once-daily fluticasone furoate 50 mcg in mild-to-moderate asthma: a 24-week placebo-controlled randomized trial. Allergy 69(11): 1522-30	- Comparator in study does not match that specified in this review protocol *Study compared fluticasone propionate to fluticasone fuorate - not a relevant comparison for this review*
Busse, W.W., O'Byrne, P.M., Bleecker, E.R. et al. (2012) Safety and tolerability of the novel inhaled corticosteroid (ICS) fluticasone furoate (FF) in combination with the longacting beta2 agonist (LABA) vilanterol (VI) administered once daily (OD) in patients with asthma. European Respiratory Journal 40(suppl56)	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Busse, William W, Bleecker, Eugene R, Bateman, Eric D et al. (2012) Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on moderate doses of inhaled corticosteroid therapy: an 8-week,	- Comparator in study does not match that specified in this review protocol *Study compared between ICS doses - not a relevant comparison in this review*

Study	Code [Reason]
randomised, placebo-controlled trial. Thorax 67(1): 35-41	
Caffey, L.F., Raissy, H.H., Marshik, P. et al. (2005) A crossover comparison of fluticasone propionate and montelukast on inflammatory indices in children with asthma. Pediatric Asthma, Allergy and Immunology 18(3): 123-130	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Canonica, G.W., Virchow, J., Kots, M. et al. (2019) Efficacy and safety of high ICS dose fixed-combination ICS/LABA/LAMA pMDI compared with ICS/LABA and ICS/LABA + LAMA in patients with uncontrolled asthma: The TRIGGER study. American Journal of Respiratory and Critical Care Medicine 199(9)	- Conference abstract
Canonical, W.G., Virchow, J.C., Singh, D. et al. (2019) Effect of high extrafine strength (HS) ICS-containing triple therapy on exacerbations in patients with severe asthma and persistent airflow limitation: Post-hoc analysis of the TRIGGER study. European Respiratory Journal 54(supplement63)	- Conference abstract
Cao, Huling, Gu, Junhua, Dai, Juan et al. (2021) Comparison of the effect of fluticasone combined with salmeterol and fluticasone alone in the treatment of pediatric asthma. Minerva pediatrics 73(5): 452-459	- No additional studies identified through reference checking
Cao, Jun-Yi; Wang, Ying-Chun; Deng, Xiao-Xia (2023) Efficacy of beta2-adrenergic receptor agonist combined with corticosteroid in the treatment of children with cough variant asthma. World journal of clinical cases 11(31): 7610-7618	- Study does not contain an intervention relevant to this review protocol *Study does not provide detail about doses used*
Cardet, J.C., Pace, W., Carroll, J. et al. (2022) Successfully Reducing Severe Asthma Exacerbations and Improving Asthma Control in a Pragmatic Study in African American/Black (AA/B) and Hispanic/Latinx (H/L) Patients with Moderate-Severe Asthma (PREPARE). Journal of Allergy and Clinical Immunology 149(2supplement): ab313	- Conference abstract
Cardet, J.C., Pace, W.D., Carroll, J.K. et al. (2022) An Add-on Reliever-Triggered Inhaled Corticosteroid Strategy Reduces Severe Asthma Exacerbations in a Real-World Study of African American/Black and Hispanic/Latinx Patients	- Conference abstract

Study	Code [Reason]
with Asthma. American Journal of Respiratory and Critical Care Medicine 205(1)	
Carroll, W D, Jones, P W, Boit, P et al. (2010) Childhood evaluation of salmeterol tolerance--a double-blind randomized controlled trial. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 21(2pt1): 336-44	- Inadequate study duration *Study treated participants for 8 weeks - inadequate to assess the outcomes listed in this review protocol*
Casale, T., Bateman, E., Aalbers, R. et al. (2017) Once-daily tiotropium Respimat add-on therapy improves lung function and asthma control in moderate symptomatic asthma, independent of baseline characteristics. European Respiratory Journal 50(supplement61)	- Conference abstract
Casale, T., Bleecker, E., Meltzer, E. et al. (2013) Phase III trials to investigate tiotropium as add-on therapy to inhaled corticosteroids for patients with symptomatic asthma: Trial design and planned statistical analyses. Allergy: European Journal of Allergy and Clinical Immunology 68(suppl97): 377	- Conference abstract
Casale, T.B., Bateman, E.D., Dahl, R. et al. (2014) Tiotropium respimat add-on therapy reduces airflow obstruction in patients with symptomatic moderate asthma, independent of Th2 inflammatory status. Journal of Allergy and Clinical Immunology 133(2suppl1): ab5	- Conference abstract
Casale, Thomas B, Aalbers, Rene, Bleecker, Eugene R et al. (2019) Tiotropium Respimat R add-on therapy to inhaled corticosteroids in patients with symptomatic asthma improves clinical outcomes regardless of baseline characteristics. Respiratory medicine 158: 97-109	- Secondary publication of an included study that does not provide any additional relevant information
Casale, Thomas B, Bateman, Eric D, Vandewalker, Mark et al. (2018) Tiotropium Respimat Add-on Is Efficacious in Symptomatic Asthma, Independent of T2 Phenotype. The journal of allergy and clinical immunology. In practice 6(3): 923-935e9	- Population not relevant to this review protocol *Secondary analysis of studies including populations not relevant to this review protocol - >20% were receiving therapies other than ICS, LABA or SABA at baseline*
Castro-Rodriguez, Jose A and Rodrigo, Gustavo J (2010) The role of inhaled corticosteroids and montelukast in children with mild-moderate asthma: results of a systematic review with	- No additional studies identified through reference checking

Study	Code [Reason]
meta-analysis. Archives of disease in childhood 95(5): 365-70	
Castro-Rodriguez, Jose A and Rodrigo, Gustavo J (2012) A systematic review of long-acting beta2-agonists versus higher doses of inhaled corticosteroids in asthma. Pediatrics 130(3): e650-7	- No additional studies identified through reference checking
Castro-Rodriguez, Jose A; Rodrigo, Gustavo J; Rodriguez-Martinez, Carlos E (2015) Principal findings of systematic reviews for chronic treatment in childhood asthma. The Journal of asthma : official journal of the Association for the Care of Asthma 52(4): 407-16	- No additional studies identified through reference checking
Castro-Rodriguez, Jose A; Rodriguez-Martinez, Carlos E; Ducharme, Francine M (2018) Daily inhaled corticosteroids or montelukast for preschoolers with asthma or recurrent wheezing: A systematic review. Pediatric pulmonology 53(12): 1670-1677	- Population not relevant to this review protocol *Review assessing ICS vs Montelukast as a first-line therapy, not second line following regular ICS as specified in the protocol*
Cates, C.J. and Lasserson, T.J. (2008) Combination formoterol and inhaled steroid as maintenance and reliever therapy versus inhaled steroid maintenance for chronic asthma in adults and children. Cochrane Database of Systematic Reviews: cd007313	- More recent systematic review included that covers the same topic
Cates, Christopher J, Jaeschke, Roman, Schmidt, Stefanie et al. (2013) Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events. The Cochrane database of systematic reviews: cd006922	- Duplicate reference
Cates, Christopher J, Jaeschke, Roman, Schmidt, Stefanie et al. (2013) Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. The Cochrane database of systematic reviews: cd006924	- No additional studies identified through reference checking
Cates, Christopher J and Karner, Charlotta (2013) Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. The Cochrane database of systematic reviews: cd007313	- More recent systematic review included that covers the same topic

Study	Code [Reason]
Cates, Christopher J and Lasserson, Toby J (2009) Combination formoterol and budesonide as maintenance and reliever therapy versus inhaled steroid maintenance for chronic asthma in adults and children. The Cochrane database of systematic reviews: cd007313	- More recent systematic review included that covers the same topic
Cates, Christopher J, Oleszczuk, Marta, Stovold, Elizabeth et al. (2012) Safety of regular formoterol or salmeterol in children with asthma: an overview of Cochrane reviews. The Cochrane database of systematic reviews 10: cd010005	- No additional studies identified through reference checking
Cates, Christopher J, Schmidt, Stefanie, Ferrer, Montse et al. (2018) Inhaled steroids with and without regular salmeterol for asthma: serious adverse events. The Cochrane database of systematic reviews 12: cd006922	- No additional studies identified through reference checking
Cates, Christopher J, Wieland, L Susan, Oleszczuk, Marta et al. (2014) Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. The Cochrane database of systematic reviews: cd010314	- No additional studies identified through reference checking
Celis, Pilar and Rada, Gabriel (2015) High-dose inhaled corticosteroids or addition of theophylline in patients with poorly controlled asthma?. Medwave 15suppl2: e6224	- Study not reported in English
Ceylan, Erkan; Gencer, Mehmet; Aksoy, Sahin (2004) Addition of formoterol or montelukast to low-dose budesonide: an efficacy comparison in short- and long-term asthma control. Respiration; international review of thoracic diseases 71(6): 594-601	- Comparator in study does not match that specified in this review protocol *Study compared low-dose ICS (400 mcg budesonide) plus montelukast to low-dose ICS (400 mcg budesonide) plus formoterol - low-dose ICS/LABA is not a comparator in this review*
Chapman, K R, Ringdal, N, Backer, V et al. (1999) Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. Canadian respiratory journal 6(1): 45-51	- Comparator in study does not match that specified in this review protocol *Study compared combination ICS/LABA to concurrent ICS + LABA - not a relevant comparison in this review*
Chapman, K.R., Van-Zyl Smit, R., Mezzi, K. et al. (2022) Efficacy of once-daily moderate- or high-dose mometasone/indacaterol/glycopyrronium	- Conference abstract

Study	Code [Reason]
(MF/IND/GLY) versus twice-daily high-dose fluticasone/salmeterol (FLU/SAL) to control nocturnal symptoms in patients (pts) with inadequately controlled asthma. European Respiratory Journal 60(supplement66)	
Chauhan, Bhupendrasinh F; Ben Salah, Raja; Ducharme, Francine M (2013) Addition of anti-leukotriene agents to inhaled corticosteroids in children with persistent asthma. The Cochrane database of systematic reviews: cd009585	- No additional studies identified through reference checking
Chauhan, Bhupendrasinh F; Chartrand, Caroline; Ducharme, Francine M (2012) Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. The Cochrane database of systematic reviews 12: cd009611	- No additional studies identified through reference checking
Chauhan, Bhupendrasinh F, Jeyaraman, Maya M, Singh Mann, Amrinder et al. (2017) Addition of anti-leukotriene agents to inhaled corticosteroids for adults and adolescents with persistent asthma. The Cochrane database of systematic reviews 3: cd010347	- No relevant studies identified from included studies
Chen, Lijuan; Huang, Manqin; Xie, Nanli (2021) The effect of montelukast sodium plus budesonide on the clinical efficacy, inflammation, and pulmonary function in children with cough variant asthma. American journal of translational research 13(6): 6807-6816	- Inadequate study duration *Study treated participants for 8 weeks - inadequate duration for assessing outcomes in this review protocol*
Chen, Xin, Kang, Ying-Bo, Wang, Li-Qing et al. (2015) Addition to inhaled corticosteroids of leukotriene receptor antagonists versus theophylline for symptomatic asthma: a meta-analysis. Journal of thoracic disease 7(4): 644-52	- Study does not contain an intervention relevant to this review protocol *Theophylline not a treatment option included in this review*
Cheng, Shih-Lung; Wang, Hao-Chien; Kuo, Sow-Hsong (2013) Early achievement and maintenance of stable asthma control using initially higher-dose inhaled corticosteroids as part of combination therapy: an open-label pilot study. Drug design, development and therapy 7: 477-84	- Study does not contain an intervention relevant to this review protocol *Participants allowed to continue baseline therapy other than ICS*
Chervinsky, Paul, Baker, James, Bensch, George et al. (2008) Patient-reported outcomes in adults with moderate to severe asthma after use of budesonide and formoterol administered via 1 pressurized metered-dose inhaler. Annals	- Data not reported in an extractable format or a format that can be analysed *Results reported without variance data*

Study	Code [Reason]
of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 101(5): 463-73	
Chipps, B., Tashkin, D., Uryniak, T. et al. (2012) Post HOC analysis of a budesonide/formoterol pressurized metered-dose inhaler (BUD/FM PMDI) study: Asthma control and study withdrawal in patients with mild to moderate asthma with versus without fixed airflow obstruction defined using 2 different criteria. Chest 142(4suppl1)	- Conference abstract
Chipps, B.E., Israel, E., Beasley, R.W. et al. (2022) Efficacy and Safety of Albuterol/Budesonide (PT027) in Mild-to-Moderate Asthma: Results of the DENALI Study. American Journal of Respiratory and Critical Care Medicine 205(1)	- Conference abstract
Chipps, Bradley E, Albers, Frank C, Reilly, Laurence et al. (2021) Efficacy and safety of as-needed albuterol/budesonide versus albuterol in adults and children aged >=4 years with moderate-to-severe asthma: rationale and design of the randomised, double-blind, active-controlled MANDALA study. BMJ open respiratory research 8(1)	- Not a peer-reviewed publication
Chong, Jimmy K and Chauhan, Bhupendrasinh F (2014) Addition of antileukotriene agents to inhaled corticosteroids in children with persistent asthma. Paediatrics & child health 19(9): 473-4	- No relevant studies identified from included studies
Chong, Jimmy, Haran, Cheyaanthan, Chauhan, Bhupendrasinh F et al. (2015) Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults. The Cochrane database of systematic reviews: cd011032	- Comparator in study does not match that specified in this review protocol *Intermittent ICS was compared to SABA as reliever medication - not relevant to this review protocol*
Chu, Fangfang; Liang, Lei; Chen, Fuzhe (2023) Effect of budesonide combined with montelukast sodium on pulmonary function parameters and immunoglobulin levels in children with bronchial asthma. Allergologia et immunopathologia 51(4): 151-157	- Inadequate study duration *Duration of treatment not reported*
Chuchalin, A G, Svensson, K, Stahl, E et al. (2002) A health-related quality-of-life comparison of formoterol (Oxis) Turbuhaler plus budesonide (Pulmicort) Turbuhaler with budesonide Turbuhaler alone and	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*

Study	Code [Reason]
noncorticosteroid treatment in asthma: a randomized clinical study in Russia. Respiration; international review of thoracic diseases 69(5): 427-33	
Cividini, Sofia, Sinha, Ian, Donegan, Sarah et al. (2021) EstablishINg the best STEp-up treatments for children with uncontrolled asthma despite INhaled corticosteroids (EINSTEIN): protocol for a systematic review, network meta-analysis and cost-effectiveness analysis using individual participant data (IPD). BMJ open 11(2): e040528	- study protocol
Cividini, Sofia, Sinha, Ian, Donegan, Sarah et al. (2023) Best step-up treatments for children with uncontrolled asthma: a systematic review and network meta-analysis of individual participant data. The European respiratory journal 62(6)	- Systematic review used as source of primary studies
Clearie, Karine L, McKinlay, Lorna, Williamson, Peter A et al. (2012) Fluticasone/Salmeterol combination confers benefits in people with asthma who smoke. Chest 141(2): 330-338	- Population not relevant to this review protocol *Participants could have received additional medication other than ICS and bronchodilators prior to inclusion*
Condemi, J J, Goldstein, S, Kalberg, C et al. (1999) The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. Salmeterol Study Group. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 82(4): 383-9	- Comparator in study does not match that specified in this review protocol *Study compared moderate-dose ICS (220 mcg fluticasone propionate twice daily) to low-dose ICS/LABA (42/88 mcg salmeterol/fluticasone twice daily) - low-dose ICS/LABA is not a relevant intervention in this review*
Confalonieri, M. (2022) In moderate-to-severe asthma, as-needed albuterol- budesonide reduced severe exacerbations vs. albuterol alone. Annals of Internal Medicine 175(9): jc106	- Conference abstract
Corren, J., Mansfield, L.E., Kaiser, K. et al. (2009) Efficacy of twice daily fluticasone propionate and formoterol fumarate combination administered using an HFA pMDI in patients with moderate to severe asthma. Journal of Allergy and Clinical Immunology 123(2suppl1): 157	- Conference abstract
Corren, Jonathan, Korenblat, Phillip E, Miller, Christopher J et al. (2007) Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose	- Study does not contain an intervention relevant to this review protocol *Study compared low-dose ICS/LABA (160/9 budesonide/formoterol twice daily) to low-dose*

Study	Code [Reason]
inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. Clinical therapeutics 29(5): 823-843	*ICS (160 mcg budesonide twice daily), formoterol alone or placebo - none of which are relevant to this review*
Cortese, Sara, Gatta, Alessia, Della Valle, Loredana et al. (2016) Fluticasone/formoterol association favors long-lasting decrease in bronchial reactivity to methacholine and weekly PEF variability. International journal of immunopathology and pharmacology 29(4): 769-774	- Population not relevant to this review protocol *Participants not presenting with asthma that is uncontrolled*
Creticos, P.S., Freidhoff, L.R., Bernstein, D.I. et al. (1999) Comparison of an inhaled corticosteroid (triamcinolone acetonide) to a long-acting bronchodilator (salmeterol), the combination, and placebo in mild-moderate adult asthmatic patients. International Archives of Allergy and Immunology 118(24): 345-346	- Data not reported in an extractable format or a format that can be analysed
Crossingham, Iain, Turner, Sally, Ramakrishnan, Sanjay et al. (2021) Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. The Cochrane database of systematic reviews 5: cd013518	- Study does not contain an intervention relevant to this review protocol *Review examines use of combination therapy as needed, not regular as specified in this review protocol*
Currie, Graeme P, Bates, Caroline E, Lee, Daniel K C et al. (2003) Effects of fluticasone plus salmeterol versus twice the dose of fluticasone in asthmatic patients. European journal of clinical pharmacology 59(1): 11-5	- Inadequate study duration *Study treated participants for 2 weeks per treatment - inadequate duration to assess outcomes listed in this protocol*
Cusack, Ruth P; Satia, Imran; O'Byrne, Paul M (2020) Asthma maintenance and reliever therapy: Should this be the standard of care?. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 125(2): 150-155	- Review article but not a systematic review
D'Urzo, A.D., Nathan, R.A., Kaiser, K. et al. (2009) Efficacy of twice daily fluticasone propionate and formoterol fumarate combination administered using an HFA pMDI in patients with mild to moderate asthma. Journal of Allergy and Clinical Immunology 123(2suppl1): 79	- Conference abstract
Dahl, R., Doherty, D.E., Corren, J. et al. (2014) Once-daily tiotropium respimat improves lung function in patients with severe symptomatic asthma independent of leukotriene modifier use. Journal of Allergy and Clinical Immunology 133(2suppl1): ab5	- Conference abstract

Study	Code [Reason]
Dahl, Ronald, Engel, Michael, Dusser, Daniel et al. (2016) Safety and tolerability of once-daily tiotropium Respimat(R) as add-on to at least inhaled corticosteroids in adult patients with symptomatic asthma: A pooled safety analysis. Respiratory medicine 118: 102-111	- Comparator in study does not match that specified in this review protocol *Secondary analysis of papers comparing ICS+LAMA combinations to placebo*
Dai, Xiaoxia, Feng, Tao, Zhang, Xuejuan et al. (2020) Budesonide/Fomoterol in combination with Montelukast in the treatment of Bronchial Asthma. Pakistan journal of medical sciences 36(7): 1688-1692	- Comparator in study does not match that specified in this review protocol *Montelukast as a sole therapy not a treatment option in this review for adults*
de Llano, Luis Perez, Naval, Elsa, Mejia, Natalia et al. (2022) Inhaled indacaterol/glycopyrronium/mometasone furoate fixed-dose combination in moderate-to-severe asthma. Expert review of respiratory medicine 16(1): 1-15	- Review article but not a systematic review
Demoly, Pascal, Louis, Renaud, Soes-Petersen, Ulrik et al. (2009) Budesonide/formoterol maintenance and reliever therapy versus conventional best practice. Respiratory medicine 103(11): 1623-32	- Comparator in study does not match that specified in this review protocol *Study compared regular ICS/formoterol plus as-needed to conventional best practice - not a specified comparator in this review protocol*
Demuro Mercon, C, Turpin, J, Santanello, N et al. (2001) Motelukast improves asthma quality of life when added to Fluticasone. Journal of allergy and clinical immunology 107(2): 248	- Conference abstract
DePietro, M., Tashkin, D.P., Chipps, B.E. et al. (2015) Effects of doubling the highest indicated dose of budesonide/ formoterol (BUD/FM) on lung function and symptoms in moderate-to-severe asthma with fixed airflow obstruction (FAO). Journal of Allergy and Clinical Immunology 135(2suppl1): ab4	- Conference abstract
Di Franco, A, Giannini, D, Bacci, E et al. (1999) Comparison of different long-term asthma treatments in subjects with mild-to-moderate asthma. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace 54(5): 390-3	- Data not reported in an extractable format or a format that can be analysed *Reported as average with range, no variance data*
Dissanayake, S., Lomax, M., Kaiser, K. et al. (2012) Asthma exacerbation with fluticasone propionate/formoterol fumarate combination therapy versus its individual components. European Respiratory Journal 40(suppl56)	- Conference abstract

Study	Code [Reason]
Dissanayake, S., Sastre, J., Papi, A. et al. (2011) Fluticasone propionate/formoterol fumarate combination therapy reduces the risk of exacerbations compared with its individual components in patients with asthma. Thorax 66(suppl4): a113	- Conference abstract
Doherty, D., Bleecker, E.R., Moroni-Zentgraf, P. et al. (2017) Tiotropium respimat: Efficacy in elderly asthma patients. American Journal of Respiratory and Critical Care Medicine 195	- Conference abstract
Ducharme, F M; Lasserson, T J; Cates, C J (2006) Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. The Cochrane database of systematic reviews: cd003137	- Systematic review used as source of primary studies
Ducharme, F.; Chauhan, B.; Chartrand, C. (2012) Intermittent versus daily inhaled corticosteroids (ICS) in children and adults with mild persistent asthma: A Cochrane review. European Respiratory Journal 40(suppl56)	- Conference abstract
Ducharme, Francine M, Ni Chroinin, Muireann, Greenstone, Ilana et al. (2010) Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. The Cochrane database of systematic reviews: cd005535	- No additional studies identified through reference checking
Dusser, D., Buhl, R., Castro, M. et al. (2014) Once-daily tiotropium respimat add-on to at least ICS in adult patients with symptomatic asthma: Pooled safety analysis. European Respiratory Journal 44(suppl58)	- Conference abstract
Edin, Heather M, Andersen, Leslie B, Schoaf, Lynne et al. (2009) Effects of fluticasone propionate and salmeterol hydrofluoroalkane inhalation aerosol on asthma-related quality of life. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 102(4): 323-7	- Data not reported in an extractable format or a format that can be analysed *Reported without variance data*
Edwards, S J, von Maltzahn, R, Naya, I P et al. (2010) Budesonide/formoterol for maintenance and reliever therapy of asthma: a meta analysis of randomised controlled trials. International journal of clinical practice 64(5): 619-27	- More recent systematic review included that covers the same topic

Study	Code [Reason]
Edwards, Steven J; Gruffydd-Jones, Kevin; Ryan, Dermot P (2007) Systematic review and meta-analysis of budesonide/formoterol in a single inhaler. Current medical research and opinion 23(8): 1809-20	- No additional studies identified through reference checking
Eickmeier, O., Bisgaard, H., Vandewalker, M. et al. (2018) Safety and efficacy of Tiotropium Respimat add-on therapy in pre-school children with symptomatic persistent asthma. Atemwegs- und Lungenkrankheiten 44(2): 80-81	- Conference abstract
Eid, Nemr S, Noonan, Michael J, Chipps, Bradley et al. (2010) Once- vs twice-daily budesonide/formoterol in 6- to 15-year-old patients with stable asthma. Pediatrics 126(3): e565-75	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Eliraz, A, Fritscher, CC, Perez, CMR et al. (2001) Budesonide and formoterol in a single inhaler quickly gains asthma control compared with fluticasone propionate in mild asthma. European respiratory journal 18(suppl33): 48s	- Conference abstract
Emad, A. (1996) Effectiveness of adding alternate-day theophylline to the treatment regimen of patients with moderate-to-severe asthma. Respiratory Care 41(6): 520-523	- Comparator in study does not match that specified in this review protocol *Study compared regular ICS to regular ICS + theophylline - not a relevant intervention in this review*
Ericsson, K, Bantje, TA, Huber, R et al. (2001) Symbicort turbohaler is more effective than fluticasone diskus in the treatment of asthma. Thorax 56(suppl3): iii63	- Conference abstract
Essilfie-Quaye, Sarah, Ito, Kazuhiro, Ito, Misako et al. (2011) Comparison of Symbicort R versus Pulmicort R on steroid pharmacodynamic markers in asthma patients. Respiratory medicine 105(12): 1784-9	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Evans, D J, Taylor, D A, Zetterstrom, O et al. (1997) A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. The New England journal of medicine 337(20): 1412-8	- Study does not contain an intervention relevant to this review protocol *Theophylline not a relevant intervention in this review protocol*
Evans, David J W, Kew, Kayleigh M, Anderson, Debbie E et al. (2015) Long-acting muscarinic antagonists (LAMA) added to inhaled	- No additional studies identified through reference checking

Study	Code [Reason]
corticosteroids (ICS) versus higher dose ICS for adults with asthma. The Cochrane database of systematic reviews: cd011437	
FitzGerald, J M, Becker, A, Sears, M R et al. (2004) Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. Thorax 59(7): 550-6	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
FitzGerald, J Mark, O'Byrne, Paul M, Bateman, Eric D et al. (2021) Safety of As-Needed Budesonide-Formoterol in Mild Asthma: Data from the Two Phase III SYGMA Studies. Drug safety 44(4): 467-478	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
FitzGerald, J.M., Kerstjens, H., Paggiaro, P. et al. (2014) Once-daily tiotropium respimat add-on to ICS+/-LABA improves control across asthma severities. European Respiratory Journal 44(suppl58)	- Conference abstract
Fitzgerald, M., O'Byrne, P.M., Bateman, E.D. et al. (2019) Number needed to treat (NNT) to have an additional patient free from a severe or moderate/severe exacerbation: Post-hoc analysis of SYGMA 1 in mild asthma. European Respiratory Journal 54(supplement63)	- Conference abstract
Fogel, Robert B, Rosario, Nelson, Aristizabal, Gustavo et al. (2010) Effect of montelukast or salmeterol added to inhaled fluticasone on exercise-induced bronchoconstriction in children. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 104(6): 511-7	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Fowler, SJ, Dempsey, AJ, Wilson, AM et al. (2001) Effects of adding either a leukotriene receptor antagonist or Theophylline to a low or moderate dose of inhaled cortiscosteroid in patients with persistent asthma. Journal of allergy and clinical immunology 107(2): 266s267	- Conference abstract
Frampton, James E (2012) Mometasone/formoterol inhalation aerosol: in asthma uncontrolled on moderate- or high-dose inhaled corticosteroids. Drugs 72(9): 1229-41	- Review article but not a systematic review
Frith, P., Kerstjens, H., Engel, M. et al. (2016) Tiotropium RESPIMAT add-on therapy to inhaled corticosteroids (ICS) + long-acting	- Conference abstract

Study	Code [Reason]
beta2-agonists (LABAS) in patients with symptomatic severe asthma: Efficacy by level of airway obstruction. Respirology 21(suppl2): 107	
Frith, P., Price, D., Bateman, E. et al. (2015) Efficacy of once-daily tiotropium respimat 5UG from five phase III trials in adults with symptomatic asthma. Respirology 20(suppl2): 137	- Conference abstract
Furlow, Bryant (2016) Combination therapy as safe as fluticasone alone in asthma. The Lancet. Respiratory medicine 4(5): 352	- Not a peer-reviewed publication
Gao, J.; Cai, F.; Wang, B. (2013) Montelukast improves air trapping, not airway remodeling, in moderate-to-severe patients with asthma: A pilot tudy. European Respiratory Journal 42(suppl57)	- Conference abstract
Gappa, Monika, Zachgo, Wolfgang, von Berg, Andrea et al. (2009) Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). Pediatric pulmonology 44(11): 1132-42	- Inadequate study duration
Garcia Garcia, M Luz, Wahn, Ulrich, Gilles, Leen et al. (2005) Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. Pediatrics 116(2): 360-9	- Comparator in study does not match that specified in this review protocol *Study compared ICS to montelukast monotherapy - not a relevant comparator in this review protocol*
Gardiner, F., Pizzichini, E., Pavord, I. et al. (2021) Captain: Effects of adding the long-acting muscarinic antagonist umeclidinium to inhaled corticosteroid/long-acting beta2-agonist therapy on symptoms in patients with inadequately controlled asthma. American Journal of Respiratory and Critical Care Medicine 203(9)	- Conference abstract
Gessner, C., Kornmann, O., Maspero, J. et al. (2020) Lower ICS dose effect on symptoms and rescue medication use of indacaterol/glycopyrronium/mometasone (IND/GLY/MF) moderate-dose vs salmeterol/fluticasone (Sal/Flu) high-dose plus tiotropium (Tio): ARGON study. European Respiratory Journal 56(supplement64)	- Conference abstract
Gessner, C., Lawrence, D., Mezzi, K. et al. (2022) Efficacy of	- Conference abstract

Study	Code [Reason]
indacaterol/glycopyrronium/mometasone (IND/GLY/MF) vs free combination of salmeterol/fluticasone (SAL/FLU) & tiotropium (TIO) in patients with uncontrolled asthma on prior LABA/ICS high-dose (GINA step 5): Results from ARGON study. European Respiratory Journal 60(supplement66)	
Gessner, Christian, Kornmann, Oliver, Maspero, Jorge et al. (2020) Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). Respiratory medicine 170: 106021	- Comparator in study does not match that specified in this review protocol *Study compares two combinations of ICS/LABA and LAMA - not a relevant comparator in this review protocol*
Ghiro, L, Zanconato, S, Rampon, O et al. (2002) Effect of montelukast added to inhaled corticosteroids on fractional exhaled nitric oxide in asthmatic children. The European respiratory journal 20(3): 630-4	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Goldsmith, David R and Keating, Gillian M (2004) Budesonide/formoterol: a review of its use in asthma. Drugs 64(14): 1597-618	- Review article but not a systematic review
Graham, L.M., Kerstjens, H.A.M., Vogelberg, C. et al. (2017) Safety and tolerability of once-daily tiotropium respimat add-on therapy in african-american patients with symptomatic persistent asthma across a range of severities. American Journal of Respiratory and Critical Care Medicine 195	- Conference abstract
Graham, LeRoy M, Kerstjens, Huib A M, Vogelberg, Christian et al. (2019) Safety of tiotropium Respimat R in black or African-American patients with symptomatic asthma. Respiratory medicine 155: 58-60	- Secondary publication of an included study that does not provide any additional relevant information
Green, R H, Brightling, C E, McKenna, S et al. (2006) Comparison of asthma treatment given in addition to inhaled corticosteroids on airway inflammation and responsiveness. The European respiratory journal 27(6): 1144-51	- Inadequate study duration *Study treated participants for four weeks per treatment - inadequate duration to assess outcomes listed in this review protocol*
Green, RH, Brightling, CE, McKenna, S et al. (2002) A placebo controlled comparison of formoterol, montelukast or higher dose of inhaled corticosteroids in subjects with symptomatic asthma despite treatment with low	- Conference abstract

Study	Code [Reason]
dose inhaled corticosteroids. Thorax 57(suppliii): iii11	
Greening, A P, Ind, P W, Northfield, M et al. (1994) Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. Lancet (London, England) 344(8917): 219-24	- Study does not contain an intervention relevant to this review protocol *Study compares low-dose (400 mcg beclomethasone plus 100 mcg salmeterol per day) ICS/LABA with 1000 mcg beclomethasone alone - low-dose ICS/LABA not a specified intervention in this review*
Greenstone, I R, Ni Chroinin, M N, Masse, V et al. (2005) Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. The Cochrane database of systematic reviews: cd005533	- More recent systematic review included that covers the same topic
Greos, L., Berger, W., Moroni-Zentgraf, P. et al. (2015) Once-daily tiotropium respimat add-on to moderate-dose inhaled corticosteroids improves lung function and asthma control in adult patients with moderate symptomatic asthma, independent of prior long-acting-2-agonist use. Chest 148(4meetingabstract)	- Conference abstract
Gross, A.S., Goldfrad, C., Hozawa, S. et al. (2013) Ethnic sensitivity assessment of fluticasone furoate (FF)/vilanterol (VI) in asthma patients in Japan and Korea: A pre-specified subgroup analysis. Respirology 18(suppl4): 157	- Conference abstract
Grosser, D and Smith, B (2002) Low-dose budesonide improved asthma control in mild asthma: adding formoterol improved control in corticosteroid-treated patients. ACP journal club 137(1): 19	- Not a peer-reviewed publication
Gupta, S; Kansal, AP; Kishan, J (2007) Comparative efficacy of combination of fluticasone and salmeterol; fluticasone, salmeterol and montelukast; fluticasone, salmeterol, and levocetirizine in moderate persistent asthma: a study of 120 patients. Chest 132(4): 512a	- Conference abstract
Haahtela, T, Tamminen, K, Malmberg, L P et al. (2006) Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: A SOMA study. The European respiratory journal 28(4): 748-55	- Study does not contain an intervention relevant to this review protocol *Study compared as-needed ICS/formoterol to as-needed formoterol alone - neither is a relevant intervention in this review*

Study	Code [Reason]
Halpin, D.M., Bateman, E.D., Moroni-Zentgraf, P. et al. (2013) Tiotropium is effective in patients with severe asthma without evidence of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 187(meetingabstracts)	- Conference abstract
Halpin, D.M.G., Bateman, E.D., Tashkin, D.P. et al. (2013) Tiotropium decreases the risk of exacerbations in patients with symptomatic asthma regardless of baseline characteristics including markers of allergic status. Thorax 68(suppl3): a149	- Conference abstract
Halpin, David M G, Hamelmann, Eckard H, Frith, Peter A et al. (2020) Comparative Responses in Lung Function Measurements with Tiotropium in Adolescents and Adults, and Across Asthma Severities: A Post Hoc Analysis. Pulmonary therapy 6(1): 131-140	- Study does not contain an intervention relevant to this review protocol *Post-hoc analysis of trials that did not contain relevant interventions or comparators*
Hamelmann, E., Boner, A., Bernstein, J. et al. (2015) Efficacy and safety assessment of once-daily tiotropium respimatw add-on to inhaled corticosteroids in adolescent patients with symptomatic asthma. Pediatric Pulmonology 50(supplement39): 55	- Conference abstract
Hamelmann, E., Boner, A., Bernstein, J. et al. (2014) 1-year efficacy and safety study of tiotropium respimat add-on to ICS in adolescent patients with symptomatic asthma. European Respiratory Journal 44(suppl58)	- Conference abstract
Hamelmann, E., Szefler, S., Vrijlandt, E.J. et al. (2018) Safety and efficacy of tiotropium in 1.5-year-old children with persistent asthmatic symptoms. Pediatric Pulmonology 53(supplement1): 100-s102	- Conference abstract
Hamelmann, E., Vogelberg, C., Voelker, B. et al. (2018) Tiotropium add-on therapy improves lung function in children and adolescents with moderate and severe symptomatic asthma, independent of markers of allergic status. Pediatrics 142(1)	- Conference abstract
Hamelmann, Eckard, Bateman, Eric D, Vogelberg, Christian et al. (2016) Tiotropium add-on therapy in adolescents with moderate asthma: A 1-year randomized controlled trial.	- Comparator in study does not match that specified in this review protocol

Study	Code [Reason]
The Journal of allergy and clinical immunology 138(2): 441-450e8	*Study added tiotropium or placebo to current ICS therapy - placebo is not a relevant comparator*
Hamelmann, Eckard and Szefler, Stanley J (2018) Efficacy and Safety of Tiotropium in Children and Adolescents. Drugs 78(3): 327-338	- Review article but not a systematic review
Hampel, Frank C; Martin, Paula; Mezzanotte, William S (2008) Early bronchodilatory effects of budesonide/formoterol pMDI compared with fluticasone/salmeterol DPI and albuterol pMDI: 2 randomized controlled trials in adults with persistent asthma previously treated with inhaled corticosteroids. The Journal of asthma : official journal of the Association for the Care of Asthma 45(4): 265-72	- Inadequate study duration *Study compared single doses of treatment in a crossover design - inadequate to assess the outcomes listed in this review protocol*
Hanania, N., Bailes, Z., Barnes, N. et al. (2020) CAPTAIN STUDY: EFFECTS OF FLUTICASONE FUROATE/UMECLIDINIUM/VILANTEROL ON FEV1 IMPROVEMENT IN ASTHMA ACCORDING TO AGE. Annals of Allergy, Asthma and Immunology 125(5supplement): 28	- Conference abstract
Hanania, N., Bailes, Z., Chang, S. et al. (2021) CAPTAIN: Effects of Cardiovascular Risk on Response to Triple Therapy in Patients With Inadequately Controlled Asthma on Inhaled Corticosteroids/Long-acting beta2-agonists (ICS/LABA). Journal of Allergy and Clinical Immunology 147(2supplement): ab58	- Conference abstract
Hanania, N., Kerwin, E., Pavord, I. et al. (2020) Step-up to high dose fluticasone furoate in combination with long-acting bronchodilator in inadequately controlled asthma: the CAPTAIN study. Journal of Allergy and Clinical Immunology 145(2supplement): ab24	- Conference abstract
Hanania, N.A., Kerwin, E., Pavord, I. et al. (2020) Step-up to high-dose fluticasone furoate in combination with long-acting bronchodilator in inadequately controlled asthma: The captain study. Allergy and Asthma Proceedings 41(6): 460	- Conference abstract
Hardy, Jo, Baggott, Christina, Fingleton, James et al. (2019) Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet (London, England) 394(10202): 919-928	*Study compared regular low-dose ICS (200 mcg budesonide twice daily) to as-needed ICS/formoterol - neither of which are relevant to this review*
Hardy, Jo, Tewhaiti-Smith, Jordan, Baggott, Christina et al. (2020) Combination budesonide/formoterol inhaler as sole reliever therapy in Maori and Pacific people with mild and moderate asthma. The New Zealand medical journal 133(1520): 61-72	- Comparator in study does not match that specified in this review protocol *Study compared regular ICS to as-needed ICS/formoterol - as-needed ICS/formoterol is not a relevant intervention in this review*
Hashimoto, S., Engel, M., Schmidt, H. et al. (2013) Once-daily tiotropium as add-on to ICS + LABA for patients with severe symptomatic asthma: Baseline characteristics in Japanese patients. Respirology 18(suppl4): 88	- Conference abstract
Hashimoto, S., Jiangtao, L., Engel, M. et al. (2017) Tiotropium respimat added on to inhaled corticosteroids reduces airflow obstruction in asian patients with moderate asthma, independent of allergic status. Respirology 22(supplement3): 166-167	- Conference abstract
Hayden, M., Engel, M., Schmidt, H. et al. (2015) Efficacy of once-daily tiotropium respimat 5 ©g from phase III trials in adults with symptomatic asthma. Journal of the American Pharmacists Association 55(2): e242-e243	- Conference abstract
Hendeles, L, Erb, TA, Bird, S et al. (2004) Post-exercise response to albuterol after addition of montelukast or salmeterol to inhaled fluticasone. Journal of allergy and clinical immunology 113(2suppl): 34	- Conference abstract
Hernandez-Trujillo, V. (2012) Intermittent or daily montelukast versus placebo for episodic asthma in children. Pediatrics 130(suppl1): 42-s43	- Conference abstract
Herring, W., Shen, Q., Zhang, Y. et al. (2022) The Relationship Between Asthma Control Questionnaire Scores and Exacerbation Risk, Resource Utilization, and Utility Values: An Analysis From the Captain Trial. Value in Health 25(12supplement): 36	- Conference abstract
Heuck, C; Heickendorff, L; Wolthers, O D (2000) A randomised controlled trial of short term	- Population not relevant to this review protocol

Study	Code [Reason]
growth and collagen turnover in asthmatics treated with inhaled formoterol and budesonide. Archives of disease in childhood 83(4): 334-9	*Participants did not have asthma that was uncontrolled*
Heyneman, Catherine A, Crafts, Rachel, Holland, Jerry et al. (2002) Fluticasone versus salmeterol/low-dose fluticasone for long-term asthma control. The Annals of pharmacotherapy 36(12): 1944-9	- Review article but not a systematic review
Hochhaus, G. and Kaiser, K. (2011) Comparing the safety and efficacy of fluticasone/ formoterol combination therapy in a single inhaler at low and moderate doses, with fluticasone and formoterol concurrently or alone, in asthma patients. Allergy: European Journal of Allergy and Clinical Immunology 66(suppl94): 585	- Conference abstract
Hoshino, M. (2009) Effects of salmeterol and fluticasone propionate combination versus fluticasone propionate on airway function and eosinophilic inflammation in mild asthma. Respirology 14(suppl3): a138	- Conference abstract
Hoshino, M.; Akitsu, K.; Ohtawa, J. (2018) Triple combination of montelukast or tiotropium and inhaled corticosteroids plus long-acting s2-agonist in persistent asthma. European Respiratory Journal 52(supplement62)	- Conference abstract
Hoshino, M., Ohtawa, J., Akitsu, K. et al. (2017) Effect of the addition of montelukast on airway inflammation and remodeling in symptomatic asthma. European Respiratory Journal 50(supplement61)	- Conference abstract
Hoshino, M; Ohtawa, J; Akitsu, K (2017) Effects of the addition of tiotropium versus montelukast on airway inflammation and remodeling in symptomatic asthma. Respirology (Carlton, Vic.) 22(suppl3): 57ao132	- Conference abstract
Hoshino, Makoto; Handa, Hiroshi; Miyazawa, Teruomi (2009) Effects of salmeterol and fluticasone propionate combination versus fluticasone propionate on airway function and eosinophilic inflammation in mild asthma. Allergology international : official journal of the Japanese Society of Allergology 58(3): 357-63	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Houghton, Catherine M, Lawson, Naomi, Borrill, Zoe L et al. (2007) Comparison of the effects of	- Inadequate study duration

Study	Code [Reason]
salmeterol/fluticasone propionate with fluticasone propionate on airway physiology in adults with mild persistent asthma. Respiratory research 8: 52	*4-week treatment period - inadequate duration to assess outcomes listed in this review protocol*
Hoy, H., Engel, M., Schmidt, H. et al. (2015) Once-daily tiotropium respimat: Safety and tolerability results from phase III trials in adults with symptomatic asthma. Journal of the American Pharmacists Association 55(2): e244	- Conference abstract
Hozawa, S., Kerstjens Huib, A.M., Tashkin, D.P. et al. (2013) Tiotropium decreases the risk of exacerbations in patients with symptomatic asthma regardless of baseline characteristics. Respirology 18(suppl4): 175	- Conference abstract
Hozawa, Soichiro, Ohbayashi, Hiroyuki, Tsuchiya, Michiko et al. (2021) Safety of Once-Daily Single-Inhaler Triple Therapy with Fluticasone Furoate/Umeclidinium/Vilanterol in Japanese Patients with Asthma: A Long-Term (52-Week) Phase III Open-Label Study. Journal of asthma and allergy 14: 809-819	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Hozawa, Soichiro; Terada, Michikazu; Hozawa, Maki (2014) Comparison of the effects of budesonide/formoterol maintenance and reliever therapy with fluticasone/salmeterol fixed-dose treatment on airway inflammation and small airway impairment in patients who need to step-up from inhaled corticosteroid monotherapy. Pulmonary pharmacology & therapeutics 27(2): 190-6	- Inadequate study duration *Study treated participants for 8 weeks - inadequate duration to assess outcomes listed in this review protocol*
Ichinose, M., Engel, M., Luhmann, R. et al. (2015) Once-daily tiotropium respimat added-on to ics for patients with moderate symptomatic asthma: Japanese patients and overall patients. Respirology 20(suppl3): 65	- Conference abstract
Ichinose, M., Ohta, K., Tohda, Y. et al. (2014) Once-daily tiotropium respimat is well tolerated and efficacious over 52 weeks in japanese patients with symptomatic asthma receiving inhaled corticosteroids (ICS) +/- long-acting B2-agonist (LABA): A randomized, double-blind, placebo-controlled study. Respirology 19(suppl3): 65	- Conference abstract
Igde, M and Anlar, FY (2009) The efficacy of montelukast monotherapy in moderate	- Conference abstract

Study	Code [Reason]
persistent asthmatic children. Iranian journal of allergy, asthma, and immunology 8(3): 169-170	
Ilowite, Jonathan, Webb, Robert, Friedman, Bruce et al. (2004) Addition of montelukast or salmeterol to fluticasone for protection against asthma attacks: a randomized, double-blind, multicenter study. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 92(6): 641-8	- Comparator in study does not match that specified in this review protocol *Participants were receiving low-dose ICS at baseline, then study compared low-dose ICS (220 mcg fluticasone per day) plus montelukast to low-dose ICS/LABA - montelukast not a relevant additional therapy in 3.2a*
Imam, Syed Fahmeed; Zafar, Saira; Oppenheimer, John J (2022) Single maintenance and reliever therapy in treatment of asthma exacerbations. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 129(6): 703-708	- No additional studies identified through reference checking
Ishiura, Yoshihisa, Fujimura, Masaki, Ohkura, Noriyuki et al. (2020) Triple Therapy with Budesonide/Glycopyrrolate/Formoterol Fumarate Improves Inspiratory Capacity in Patients with Asthma-Chronic Obstructive Pulmonary Disease Overlap. International journal of chronic obstructive pulmonary disease 15: 269-277	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Ishiura, Yoshihisa, Fujimura, Masaki, Ohkura, Noriyuki et al. (2019) Effect of triple therapy in patients with asthma-COPD overlap. International journal of clinical pharmacology and therapeutics 57(8): 384-392	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Jabbal, S; Manoharan, A; Lipworth, B J (2017) Bronchoprotective tolerance with indacaterol is not modified by concomitant tiotropium in persistent asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 47(10): 1239-1245	- Inadequate study duration *Study treated participants for 4 weeks per treatment - inadequate duration to assess outcomes listed in this review protocol*
Jabbal, Sunny; Kuo, Chris RuiWen; Lipworth, Brian (2020) Randomized controlled trial of triple versus dual inhaler therapy on small airways in smoking asthmatics. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 50(10): 1140-1147	- Inadequate study duration *Study treated participants for 4 weeks per treatment - inadequate duration to assess outcomes in this review protocol*
Janeva, EJ, Goseva, Z, Gjorchev, A et al. (2015) The effect of combined therapy ICS/LABA and ICS/LABA plus montelukast in patients with uncontrolled severe persistent asthma based on	- Population not relevant to this review protocol *Participants had severe asthma, not covered in the scope of this guideline*

Study	Code [Reason]
the serum IL-13 and FEV1. Open access Macedonian journal of medical sciences 3(2): 268-272	
Jat, Gokul Chand; Mathew, Joseph L; Singh, Meenu (2006) Treatment with 400 microg of inhaled budesonide vs 200 microg of inhaled budesonide and oral montelukast in children with moderate persistent asthma: randomized controlled trial. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 97(3): 397-401	- Data not reported in an extractable format or a format that can be analysed *Data reported graphically or without variance*
Jehan, N; Rehman, MU; Zarkoon, MH (2014) To determine the efficacy of inhaled corticosteroids compared to montelukast in reducing exacerbation in uncontrolled asthma in children 6 months to 5 years. Pakistan journal of medical and health sciences 8(3): 662-666	- No relevant outcomes identified
Jenkins, C R, Thien, F C K, Wheatley, J R et al. (2005) Traditional and patient-centred outcomes with three classes of asthma medication. The European respiratory journal 26(1): 36-44	- Inadequate study duration *Crossover study with 6 weeks per treatment - inadequate to assess outcomes listed in this review protocol*
Jenkins, C., Eriksson, G., Bateman, E.D. et al. (2013) Efficacy of budesonide/formoterol maintenance and reliever therapy in mild asthma. European Respiratory Journal 42(suppl57)	- Conference abstract
Jenkins, Christine (2019) Barriers to achieving asthma control in adults: evidence for the role of tiotropium in current management strategies. Therapeutics and clinical risk management 15: 423-435	- Review article but not a systematic review
Jenkins, Christine R, Bateman, Eric D, Sears, Malcolm R et al. (2020) What have we learnt about asthma control from trials of budesonide/formoterol as maintenance and reliever?. Respirology (Carlton, Vic.) 25(8): 804-815	- Review article but not a systematic review
Jenkins, Christine, Kolarikova, Renata, Kuna, Piotr et al. (2006) Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology (Carlton, Vic.) 11(3): 276-86	- Data not reported in an extractable format or a format that can be analysed *Data reported without variance*

Study	Code [Reason]
Jiangtao, L., Crawford, J., Jacques, L. et al. (2013) Efficacy and safety of once-daily fluticasone furoate/vilanterol 200/25 MCG compared with twice-daily fluticasone propionate 500 MCG in asthma patients of Asian ancestry. Respirology 18(suppl4): 111	- Conference abstract
Johansson, G., McIvor, R.A., D'Ambrosio, F.P. et al. (2001) Comparison of salmeterol/fluticasone propionate combination with budesonide in patients with mild-to-moderate asthma. Clinical Drug Investigation 21(9): 633-642	- Comparator in study does not match that specified in this review protocol *Study compared low-dose ICS/LABA to moderate-dose ICS monotherapy - not a relevant comparison in this review*
Joos, S, Miksch, A, Szecsenyi, J et al. (2008) Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. Thorax 63(5): 453-62	- No additional studies identified through reference checking
Jorup, Carin; Lythgoe, Dan; Bisgaard, Hans (2018) Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma. The European respiratory journal 51(1)	- No additional studies identified through reference checking
Juniper, E F, Svensson, K, O'Byrne, P M et al. (1999) Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. The European respiratory journal 14(5): 1038-43	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Kaiser, Harold, Parasuraman, Bhash, Boggs, Robert et al. (2008) Onset of effect of budesonide and formoterol administered via one pressurized metered-dose inhaler in patients with asthma previously treated with inhaled corticosteroids. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 101(3): 295-303	- Study does not contain an intervention relevant to this review protocol *Secondary analysis of studies comparing low-dose ICS/LABA (160/9 mcg budesonide/formoterol twice daily) to low-dose ICS (160 mcg budesonide twice daily) alone - neither of which are relevant to this review*
Kaiser, Sunitha V, Huynh, Tram, Bacharier, Leonard B et al. (2016) Preventing Exacerbations in Preschoolers With Recurrent Wheeze: A Meta-analysis. Pediatrics 137(6)	- Conference abstract
Kankaanranta, Hannu, Lahdensuo, Aarne, Moilanen, Eeva et al. (2004) Add-on therapy options in asthma not adequately controlled by inhaled corticosteroids: a comprehensive review. Respiratory research 5: 17	- No additional studies identified through reference checking

Study	Code [Reason]
Kanniess, F, Richter, K, Bohme, S et al. (2002) Montelukast versus fluticasone: effects on lung function, airway responsiveness and inflammation in moderate asthma. The European respiratory journal 20(4): 853-8	- Population not relevant to this review protocol *Participants were not receiving ICS at baseline*
Kaplan, A., Mark FitzGerald, J., Jugovic, B. et al. (2019) Tiotropium has similar efficacy to long-acting B2-agonists and greater efficacy than leukotriene receptor antagonists as add-on to ics in adults with asthma: A systematic review. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine 3(supplement1): 5	- Conference abstract
Karaman, O, Sunneli, L, Uzuner, N et al. (2004) Evaluation of montelukast in 8 to 14 year old children with mild persistent asthma and compared with inhaled corticosteroids. Allergologia et immunopathologia 32(1): 21-7	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Kardos, P (2013) Budesonide/formoterol maintenance and reliever therapy versus free-combination therapy for asthma: a real-life study. Pneumologie (Stuttgart, Germany) 67(8): 463-70	- Study design not relevant to this review protocol *Not an RCT*
Kavuru, M, Melamed, J, Gross, G et al. (2000) Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: a randomized, double-blind, placebo-controlled trial. The Journal of allergy and clinical immunology 105(6pt1): 1108-16	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Kawai, M, Kempsford, R, Pullerits, T et al. (2007) Comparison of the efficacy of salmeterol/fluticasone propionate combination in Japanese and Caucasian asthmatics. Respiratory medicine 101(12): 2488-94	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Keith, P, D' Urzo, A, Stepner, N et al. (2001) Fluticasone/salmeterol combination (FSC) is safe and provides effective long-term (52 week) control in the management of patients with persistent asthma (PA). European respiratory journal 18(suppl33): 176s	- Conference abstract
Kelly, H.W., Lincourt, W., Kral, K. et al. (2010) The relationship between FEF25-75% and FEV1 following treatment with fluticasone propionate or fluticasone propionate/salmeterol	- Conference abstract

Study	Code [Reason]
via Diskus. Annals of Allergy, Asthma and Immunology 105(5): a48	
Kelsen, S G, Church, N L, Gillman, S A et al. (1999) Salmeterol added to inhaled corticosteroid therapy is superior to doubling the dose of inhaled corticosteroids: a randomized clinical trial. The Journal of asthma : official journal of the Association for the Care of Asthma 36(8): 703-15	- Comparator in study does not match that specified in this review protocol *Study compared moderate-dose ICS to low-dose ICS/LABA combination - not a relevant comparator in this review protocol*
Kemp, J.P., Cook, D.A., Incaudo, G.A. et al. (1998) Salmeterol improves quality of life in patients with asthma requiring inhaled corticosteroids. Journal of Allergy and Clinical Immunology 101(2i): 188-195	- Study does not contain an intervention relevant to this review protocol *Study maintained participants on their usual ICS treatment which ranged from 252-840 mcg per day beclomethasone, 1000-2000 mcg per day flunisolide or 600-1600 mcg triamcinolone, constituting low, moderate and high-dose ICS - low-dose ICS is not a relevant intervention in this review protocol*
Kerstjens, H., Bleecker, E., Meltzer, E. et al. (2014) Tiotropium as add-on to inhaled corticosteroids significantly improves asthma control as reflected by the ACQ responder rate. Respirology 19(suppl2): 78	- Conference abstract
Kerstjens, H., Bleecker, E., Meltzer, E. et al. (2014) Tiotropium as add-on therapy to inhaled corticosteroids for patients with symptomatic asthma: Lung function and safety. Respirology 19(suppl2): 78	- Conference abstract
Kerstjens, H., Paggiaro, P., Vandewalker, M. et al. (2012) Tiotropium provides sustained bronchodilation in asthmatics with persistent airflow obstruction uncontrolled despite treatment in accordance with guidelines. European Respiratory Journal 40(suppl56)	- Conference abstract
Kerstjens, H.A., Lawrence, D., Mezzi, K. et al. (2022) Effect of once daily (o.d.) mometasone/indacaterol/glycopyrronium (MF/IND/GLY) vs o.d. MF/IND and twice daily (b.i.d.) fluticasone/salmeterol (FLU/SAL) with respect to age, age at asthma-onset and BMI at baseline: Subgroup analysis from IRIDIUM study. European Respiratory Journal 60(supplement66)	- Conference abstract
Kerstjens, H.A., Pavord, I.D., Peachey, G. et al. (2020) Captain study: Simultaneous step-up to	- Conference abstract

Study	Code [Reason]
high dose fluticasone furoate and addition of umeclidinium for the treatment of inadequately controlled asthma. American Journal of Respiratory and Critical Care Medicine 201(1)	
Kerstjens, H.A., van Zyl-Smit, R., D'Andrea, P. et al. (2021) Assessment of cortisol levels with once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma: Post hoc analysis from the iridium study. American Journal of Respiratory and Critical Care Medicine 203(9)	- Conference abstract
Kerstjens, H.A.M., Abbott, C., Boulet, L.-P. et al. (2021) CAPTAIN: Effects of triple therapy on FEV1 response in patients with inadequately controlled asthma on ICS/LABA. European Respiratory Journal 58(suppl65)	- Conference abstract
Kerstjens, H.A.M., Bleecker, E., Meltzer, E. et al. (2013) Tiotropium as add-on to inhaled corticosteroids significantly improves asthma control as reflected by the ACQ responder rate. European Respiratory Journal 42(suppl57)	- Conference abstract
Kerstjens, H.A.M., Bleecker, E., Meltzer, E. et al. (2013) Tiotropium as add-on therapy to inhaled corticosteroids for patients with symptomatic asthma: Lung function and safety. European Respiratory Journal 42(suppl57)	- Conference abstract
Kerstjens, H.A.M., Engel, M., Moroni-Zentgraf, P. et al. (2013) Tiotropium added to inhaled corticosteroids and long-acting b2-agonists reduces episodes of asthma worsening, irrespective of selected patient baseline characteristics. Allergy: European Journal of Allergy and Clinical Immunology 68(suppl97): 41	- Conference abstract
Kerstjens, H.A.M., Maspero, J.F., Chapman, K.R. et al. (2021) Efficacy of mometasone/indacaterol/glycopyrronium (MF/IND/GLY) on lung function and exacerbations in patients with inadequately controlled asthma with moderate-dose ICS/LABA therapy (on GINA step 4) prior to study entry: Results from IRIDIUM study. European Respiratory Journal 58(suppl65)	- Conference abstract

Study	Code [Reason]
Kerstjens, H.A.M., Paggiaro, P., Vandewalker, M. et al. (2012) Tiotropium provides sustained bronchodilation in patients with uncontrolled asthma and persistent airflow obstruction despite treatment in accordance with guidelines. Respirology 17(suppl2): 6	- Conference abstract
Kerstjens, H.A.M., Tashkin, D.P., Engel, M. et al. (2013) Tiotropium decreases the risk of exacerbations in patients with symptomatic asthma regardless of baseline characteristics. American Journal of Respiratory and Critical Care Medicine 187(meetingabstracts)	- Conference abstract
Kerstjens, H.A.M., Van Zyl-Smit, R., Chapman, K. et al. (2021) Efficacy of mometasone/indacaterol/glycopyrronium (MF/IND/GLY) versus fluticasone/salmeterol(FLU/SAL) in ex-smoker and never smoker patients with inadequately controlled asthma: Post hoc analysis ofIRIDIUM study. European Respiratory Journal 58(suppl65)	- Conference abstract
Kerstjens, HAM, Engel, M, Dahl, R et al. (2014) Tiotropium Respimat® add-on therapy to inhaled corticosteroids (ICS) + long-acting B2-agonists (LABAS) in patients with symptomatic severe asthma: efficacy by level of airway obstruction (Abstract). American journal of respiratory and critical care medicine 189: a1312	- Conference abstract
Kerstjens, Huib A M, Disse, Bernd, Schroder-Babo, Winfried et al. (2011) Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. The Journal of allergy and clinical immunology 128(2): 308-14	- Inadequate study duration *Study treated participants for 8 weeks per treatment - inadequate duration to assess the outcomes listed in this review protocol*
Kerstjens, Huib A M, Engel, Michael, Dahl, Ronald et al. (2012) Tiotropium in asthma poorly controlled with standard combination therapy. The New England journal of medicine 367(13): 1198-207	- Population not relevant to this review protocol *Participants were receiving treatments other than ICS/LABA at baseline (theophylline, leukotriene modifiers, anti-IgE antibodies and oral corticoids)*
Kerstjens, Huib A M, Moroni-Zentgraf, Petra, Tashkin, Donald P et al. (2016) Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway	- Study does not contain an intervention relevant to this review protocol *Study treated participants with LAMA in addition to their current high-dose ICS therapy (>800 mcg budesonide equiv.) - not relevant to this*

Study	Code [Reason]
obstruction, and allergic status. Respiratory medicine 117: 198-206	*review protocol (low-moderate dose ICS + LAMA specified in protocol)*
Kerstjens, Huib A M and O'Byrne, Paul M (2016) Tiotropium for the treatment of asthma: a drug safety evaluation. Expert opinion on drug safety 15(8): 1115-24	- Review article but not a systematic review
Kerwin, Edward M, Oppenheimer, John J, LaForce, Craig et al. (2009) Efficacy and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler in adults and adolescents with asthma previously stable with twice-daily budesonide/ formoterol dosing. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 103(1): 62-72	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Kerwin, Edward, Barnes, Neil, Gibbs, Michael et al. (2018) Fluticasone furoate/vilanterol once daily improves night-time awakenings in asthma patients with night symptoms: Post hoc analyses of three randomized controlled trials. The Journal of asthma : official journal of the Association for the Care of Asthma 55(8): 890-897	- Secondary publication of an included study that does not provide any additional relevant information
Kerwin, Edward, Dorinsky, Paul, Patel, Mehul et al. (2022) A randomized controlled trial of glycopyrrolate administered by metered dose inhaler in patients with uncontrolled asthma despite ICS/LABA treatment. The Journal of asthma : official journal of the Association for the Care of Asthma 59(7): 1420-1432	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA + LAMA combinations to placebo - not a relevant comparator in this review*
Kerwin, Edward, Pascoe, Steven, Bailes, Zelie et al. (2020) A phase IIb, randomised, parallel-group study: the efficacy, safety and tolerability of once-daily umeclidinium in patients with asthma receiving inhaled corticosteroids. Respiratory research 21(1): 148	- Population not relevant to this review protocol *Participants could have been receiving LAMA in addition to ICS/LABA at baseline - number of participants not reported*
Kew, Kayleigh M and Dahri, Karen (2016) Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. The Cochrane database of systematic reviews: cd011721	- No additional studies identified through reference checking
Kew, Kayleigh M, Evans, David J W, Allison, Debbie E et al. (2015) Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-	- Duplicate reference

Study	Code [Reason]
acting beta2-agonists (LABA) for adults with asthma. The Cochrane database of systematic reviews: cd011438	
Kew, Kayleigh M, Karner, Charlotta, Mindus, Stephanie M et al. (2013) Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. The Cochrane database of systematic reviews: cd009019	- No additional studies identified through reference checking
Kim, L., Saleh, C., Whalen-Browne, A. et al. (2021) Triple (ICS/LABA/LAMA) vs. Dual (ICS/LABA) therapy for persistent, uncontrolled asthma: A systematic review and meta-analysis. American Journal of Respiratory and Critical Care Medicine 203(9)	- Conference abstract
Kim, Lisa H Y, Saleh, Carol, Whalen-Browne, Anna et al. (2021) Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma: A Systematic Review and Meta-analysis. JAMA 325(24): 2466-2479	- Systematic review used as source of primary studies
Kim, Y.H. and Lee, S.W. (2014) Long-acting anticholinergic agents in patients with uncontrolled asthma: A systematic review & meta-analysis. Respirology 19(suppl3): 68	- Conference abstract
Kips, J C, O'Connor, B J, Inman, M D et al. (2000) A long-term study of the antiinflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. American journal of respiratory and critical care medicine 161(3pt1): 996-1001	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Knorr, B, Matz, J, Bernstein, J A et al. (1998) Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. Pediatric Montelukast Study Group. JAMA 279(15): 1181-6	- Population not relevant to this review protocol *Participants were not receiving ICS at baseline*
Kondo, Naomi, Katsunuma, Toshio, Odajima, Yasuhei et al. (2006) A randomized open-label comparative study of montelukast versus theophylline added to inhaled corticosteroid in asthmatic children. Allergology international : official journal of the Japanese Society of Allergology 55(3): 287-93	- Comparator in study does not match that specified in this review protocol *ICS plus theophylline was the comparator - not relevant to this review*

Study	Code [Reason]
Koopmans, J G, Lutter, R, Jansen, H M et al. (2006) Adding salmeterol to an inhaled corticosteroid: long term effects on bronchial inflammation in asthma. Thorax 61(4): 306-12	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Korenblat, Phillip E and Rosenwasser, Lanny J (2010) Budesonide/formoterol pressurized metered-dose inhaler for patients with persistent asthma. Allergy and asthma proceedings 31(3): 190-202	- Review article but not a systematic review
Kornmann, O., Mucsi, J., Kolosa, N. et al. (2019) Once-daily low-dose indacaterol/mometasone via Breezhaler reduces exacerbations in patients with inadequately controlled asthma: Phase III QUARTZ Study. Thorax 74(supplement2): a209-a210	- Conference abstract
Kostikas, K., Kerstjens, H.A.M., Maspero, J.F. et al. (2021) Mometasone/indacaterol/glycopyrronium (MF/IND/GLY)improves lung function and reduces exacerbations in patients with asthma, independent of baseline airflow limitation: Results from IRIDIUM study. European Respiratory Journal 58(suppl65)	- Conference abstract
Kovesi, T. (2011) In children and adolescents with mild persistent asthma, daily beclomethasone reduces treatment failure compared with rescue beclomethasone plus albuterol. Evidence-Based Medicine 16(6): 183-184	- Not a peer-reviewed publication
Kumar, Vikram, Ramesh, P, Lodha, Rakesh et al. (2007) Montelukast vs. inhaled low-dose budesonide as monotherapy in the treatment of mild persistent asthma: a randomized double blind controlled trial. Journal of tropical pediatrics 53(5): 325-30	- Population not relevant to this review protocol *Participants were not receiving ICS at baseline*
Kuna, P, Chuchalin, A, Ringdal, N et al. (2001) Low-dose single-inhaler budesonide/formoterol administered once daily is effective in mild-persistent asthma. European respiratory journal 18(suppl33): 158s	- Conference abstract
Kuna, Piotr (2010) Treatment comparison of budesonide/formoterol with salmeterol/fluticasone propionate in adults aged > or =16 years with asthma: post hoc analysis of	- Secondary publication of an included study that does not provide any additional relevant information

Study	Code [Reason]
a randomized, double-blind study. Clinical drug investigation 30(9): 565-79	
Kuo, C.R.W.; Jabbal, S.; Lipworth, B. (2019) Comparison of ics containing open triple and dual therapy on small airways function in the smoking asthma phenotype. Thorax 74(supplement2): a211-a212	- Conference abstract
Kurashima, Kazuyoshi, Kagiyama, Naho, Takayanagi, Noboru et al. (2011) Comparison of high-dose salmeterol/fluticasone and moderate-dose salmeterol/fluticasone plus low-dose mometasone in patients with severe persistent asthma. Respirology (Carlton, Vic.) 16(5): 784-9	- Comparator in study does not match that specified in this review protocol *Comparator was ICS/LABA + ICS - not relevant to this review protocol*
LaForce, C., Meltzer, E., Nathan, R. et al. (2010) Effect of treatment with mometasone furoate/Formoterol combination (MF/F) on rescue medication use. Journal of Allergy and Clinical Immunology 125(2suppl1): ab194	- Conference abstract
Laforce, C., Meltzer, E.O., Nathan, R.A. et al. (2011) Greater reduction in asthma symptom frequency during treatment with mometasone furoate/formoterol combination versus monocomponents and placebo. Journal of Allergy and Clinical Immunology 127(2suppl1): ab158	- Conference abstract
LaForce, C., Nelson, H., Bonuccelli, C. et al. (2010) Effect on pulmonary function of budesonide/formoterol pressurized metered-dose inhaler versus budesonide by age group in randomized, controlled trials of patients with asthma. Allergy and Asthma Proceedings 31(2): 167	- Conference abstract
Lane, M. (2010) Tiotropium bromide in asthma patients: An alternative to inhaled long-acting beta-agonists?. Journal of the Royal College of Physicians of Edinburgh 40(4): 321-322	- Conference abstract
Lanier, B, Goode Sellers, ST, Edwards, LD et al. (2001) Low dose Fluticasone Propionate provides superior improvement in asthma symptom control and greater physician and patient satisfaction compared to Montelukast. Journal of allergy and clinical immunology 107(2): 101	- Conference abstract

Study	Code [Reason]
Lasserson, T.J.; Cates, C.J.; Ferrara, G. (2007) Combination fluticasone and salmeterol vesus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. Cochrane Database of Systematic Reviews: cd004106	- study protocol
Laviolette, M, Malmstrom, K, Lu, S et al. (1999) Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. American journal of respiratory and critical care medicine 160(6): 1862-8	- Comparator in study does not match that specified in this review protocol *Participants were receiving low-dose ICS at baseline, then study added montelukast or increased ICS dose - montelukast is not a relevant comparator in 3.2a*
Lazarinis, Nikolaos, Jorgensen, Leif, Ekstrom, Tommy et al. (2014) Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. Thorax 69(2): 130-6	- Study does not contain an intervention relevant to this review protocol *Study compared as-needed SABA to regular ICS plus as-needed SABA or ICS plus LABA as-needed - none of which are relevant interventions in this review*
Leather, D., Vestbo, J., Bakerly, N.D. et al. (2017) Late Breaking Abstract-Effectiveness of Fluticasone furoate/vilanterol (FF/VI) compared to usual care (UC) in patients with asthma: The Salford Lung Study (SLS). European Respiratory Journal 50(supplement61)	- Conference abstract
Lee, J., Oh, M., Lee, B. et al. (2010) Increased doses of inhaled corticosteroids versus addition of long-acting beta2 agonists for treatment of asthma. Allergy: European Journal of Allergy and Clinical Immunology 65(suppl92): 553-554	- Conference abstract
Lee, Laurie A, Yang, Shuying, Kerwin, Edward et al. (2015) The effect of fluticasone furoate/umeclidinium in adult patients with asthma: a randomized, dose-ranging study. Respiratory medicine 109(1): 54-62	- Inadequate study duration *Study treated participants for 14 days per treatment in crossover design - inadequate duration to assess outcomes listed in this protocol*
Lee, Yu-Sung, Lin, Horng-Chyuan, Huang, Chien-Da et al. (2011) Efficacy and tolerability of salmeterol/fluticasone propionate versus fluticasone propionate in asthma patients: a randomized, double-blind study. Chang Gung medical journal 34(4): 382-94	- Inadequate study duration *Study treated participants for 2 weeks - inadequate duration to assess outcomes listed in this review protocol*
Leidy, Nancy Kline, Gutierrez, Benjamin, Lampl, Kathy et al. (2009) Can patients with asthma feel inhaler therapy working right away? Two	- Inadequate study duration

Study	Code [Reason]
clinical trials testing the effect of timing of assessment on patient perception. The Journal of asthma : official journal of the Association for the Care of Asthma 46(10): 1006-12	*Study treated participants for 2 weeks per treatment - inadequate duration to assess the outcomes listed in this review protocol*
Leigh, R, Vethanayagam, D, Yoshida, M et al. (2002) Effects os montelukast and budesonide alone or in combination on allergen induced early and late asthmatic responses, and post-allergen airway hyperresponsiveness. American journal of respiratory and critical care medicine 165(suppl8): a216	- Conference abstract
Lemanske, Robert F Jr, Mauger, David T, Sorkness, Christine A et al. (2010) Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. The New England journal of medicine 362(11): 975-85	- Population not relevant to this review protocol *Participants were receiving treatments other than ICS/LABA at baseline*
Li, Hong-tao, Zhang, Tian-tuo, Zhou, Hong et al. (2007) Combination therapy with the single inhaler salmeterol/fluticasone propionate versus increased doses of inhaled corticosteroids in patients with asthma. Respiration; international review of thoracic diseases 74(1): 33-43	- Systematic review used as source of primary studies
Li, Hua; Dong, Tao; Luan, Jinling (2023) Efficacy and safety of fluticasone propionate/salmeterol and fluticasone propionate monotherapy in step-up treatment of childhood asthma: A systematic review and meta-analysis. Heart & lung : the journal of critical care 63: 23-34	- Systematic review used as source of primary studies
Li, J.S., Qaqundah, P.Y., Weinstein, S.F. et al. (2010) Fluticasone propionate/salmeterol combination in children with asthma: Key cardiac and overall safety results. Clinical Research and Regulatory Affairs 27(3): 87-95	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Li, X, Ward, C, Thien, F et al. (1999) An antiinflammatory effect of salmeterol, a long-acting beta(2) agonist, assessed in airway biopsies and bronchoalveolar lavage in asthma. American journal of respiratory and critical care medicine 160(5pt1): 1493-9	- No relevant outcomes identified
Lim, S, Jatakanon, A, Gordon, D et al. (2000) Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. Thorax 55(10): 837-41	- Comparator in study does not match that specified in this review protocol *Comparing increased ICS dose to ICS plus theophylline - not relevant to this review*

Study	Code [Reason]
Lin, Jiang-Tao, Chen, Ping, Zhou, Xin et al. (2012) Budesonide/formoterol maintenance and reliever therapy in Chinese patients with asthma. Chinese medical journal 125(17): 2994-3001	- Secondary publication of an included study that does not provide any additional relevant information
Lin, Jiangtao, Zhou, Xin, Wang, Changzheng et al. (2018) Symbicort R Maintenance and Reliever Therapy (SMART) and the evolution of asthma management within the GINA guidelines. Expert review of respiratory medicine 12(3): 191-202	- Review article but not a systematic review
Lipworth, Brian J, Basu, Kaninika, Donald, Helen P et al. (2013) Tailored second-line therapy in asthmatic children with the Arg(16) genotype. Clinical science (London, England : 1979) 124(8): 521-8	- Population not relevant to this review protocol *Participants could have been receiving therapies other than SABA, ICS or LABA before inclusion*
Lotvall, J., Bleecker, E., Busse, W. et al. (2012) Efficacy and safety of once-daily (OD) fluticasone furoate (FF) in patients with persistent asthma: A 24-week randomised trial. European Respiratory Journal 40(suppl56)	- Conference abstract
Lotvall, Jan, Bateman, Eric D, Busse, William W et al. (2014) Comparison of vilanterol, a novel long-acting beta2 agonist, with placebo and a salmeterol reference arm in asthma uncontrolled by inhaled corticosteroids. Journal of negative results in biomedicine 13(1): 9	- Comparator in study does not match that specified in this review protocol *Study compared vilanterol to salmeterol to placebo - within drug comparisons not relevant to this review*
Lotvall, Jan, Bleecker, Eugene R, Busse, William W et al. (2014) Efficacy and safety of fluticasone furoate 100 mug once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised trial. Respiratory medicine 108(1): 41-9	- Comparator in study does not match that specified in this review protocol *Study compared 100 mcg fluticasone per day to 250 mcg fluticasone twice daily - low vs moderate-high dose ICS is not a relevant comparison in this review*
Louis, R, Joos, G, Michils, A et al. (2009) A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. International journal of clinical practice 63(10): 1479-88	- Comparator in study does not match that specified in this review protocol *Study compared SMART therapy with conventional best practise at physicians discretion - not a comparator listed in this review protocol*
Lundback, Bo, Ronmark, Eva, Lindberg, Anne et al. (2006) Control of mild to moderate asthma over 1-year with the combination of salmeterol	- Population not relevant to this review protocol *Participants could have received additional medication other than ICS and bronchodilators prior to inclusion*

Study	Code [Reason]
and fluticasone propionate. Respiratory medicine 100(1): 2-10	
Lundborg, Mikael, Wille, Soren, Bjermer, Leif et al. (2006) Maintenance plus reliever budesonide/formoterol compared with a higher maintenance dose of budesonide/formoterol plus formoterol as reliever in asthma: an efficacy and cost-effectiveness study. Current medical research and opinion 22(5): 809-21	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Luo, Huiling, Han, Hongmei, Liu, Xiaoli et al. (2020) Efficacy and safety of montelukast sodium combined with fluticasone in the treatment of adult bronchial asthma: A protocol for systematic review and meta-analysis. Medicine 99(52): e23453	- study protocol
Lutfeali, S. and Parrish, C. (2019) The efficacy and safety of fluticasone/salmeterol compared to fluticasone in children younger than four years of age. Pediatrics 144: 56-s57	- Conference abstract
Lyseng-Williamson, Katherine A and Simpson, Dene (2008) Budesonide/Formoterol pressurized metered-dose inhaler. Drugs 68(13): 1855-64	- Review article but not a systematic review
Mahr, T.A. and Mumm, J. (2011) Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma. Pediatrics 128(suppl3): 129-s130	- Conference abstract
Mahr, T and Eppley, J (2017) Serious Asthma Events with Budesonide plus Formoterol Vs. Budesonide Alone. Pediatrics 140: S220	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Makela, Mika J, Malmberg, L Pekka, Csonka, Peter et al. (2012) Salmeterol and fluticasone in young children with multiple-trigger wheeze. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 109(1): 65-70	- Population not relevant to this review protocol *Participants were not receiving regular ICS at baseline*
Mansfield, L., Harper III, T., Moroni-Zentgraf, P. et al. (2015) Once-daily tiotropium respimat add-on to maintenance therapy in adolescent patients with symptomatic asthma: Pooled safety analysis. Annals of Allergy, Asthma and Immunology 115(5suppl1): a55	- Conference abstract

Study	Code [Reason]
Mansfield, Lyndon, Yiu, Gloria, Sakov, Anat et al. (2017) A 6-month safety and efficacy study of fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers in persistent asthma. Allergy and asthma proceedings 38(4): 264-276	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Mansur, AH and Kaiser, K (2013) Long-term safety and efficacy of fluticasone/formoterol combination therapy in asthma. Journal of aerosol medicine and pulmonary drug delivery 26(4): 190-199	- Comparator in study does not match that specified in this review protocol *Study compared two doses of ICS/LABA - not a relevant comparator in this review*
Martinez, Fernando D, Chinchilli, Vernon M, Morgan, Wayne J et al. (2011) Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. Lancet (London, England) 377(9766): 650-7	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Maselli, D., Chang, S., Fowler, A. et al. (2021) CAPTAIN: Effects of Body Mass Index (BMI) on Response to Triple Therapy in Patients With Inadequately Controlled Asthma on Inhaled Corticosteroids/Long-acting beta2-agonists (ICS/LABA). Journal of Allergy and Clinical Immunology 147(2supplement): ab57	- Conference abstract
Masoli, M, Weatherall, M, Holt, S et al. (2005) Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. Thorax 60(9): 730-4	- Systematic review used as source of primary studies
Maspero, J F, Duenas-Meza, E, Volovitz, B et al. (2001) Oral montelukast versus inhaled beclomethasone in 6- to 11-year-old children with asthma: results of an open-label extension study evaluating long-term safety, satisfaction, and adherence with therapy. Current medical research and opinion 17(2): 96-104	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Maspero, J., Kerstjens, H.A.M., Chapman, K.R. et al. (2021) Efficacy of mometasone/indacaterol/glycopyrronium (MF/IND/GLY) on lung function and exacerbations in patients with inadequately controlled asthma with high-dose ICS/LABA therapy (on GINA step 5) prior to study entry: Results from IRIDIUM study. European Respiratory Journal 58(suppl65)	- Conference abstract

Study	Code [Reason]
Maspero, J., Meltzer, E., Nathan, R. et al. (2011) Exposure-adjusted rates of treatment-related adverse events during mometasone furoate/ formoterolasthma treatment: Post hocanalysis of 6 mometasone furoate/formoterol TRIALS. Annals of Allergy, Asthma and Immunology 107(5suppl1): a40	- Conference abstract
Maspero, Jorge, Guerra, Frances, Cuevas, Francisco et al. (2008) Efficacy and tolerability of salmeterol/fluticasone propionate versus montelukast in childhood asthma: A prospective, randomized, double-blind, double-dummy, parallel-group study. Clinical therapeutics 30(8): 1492-504	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA to montelukast monotherapy - not a relevant comparator for this review*
Matz, J, Emmett, A, Rickard, K et al. (2001) Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: an analysis of asthma exacerbations. The Journal of allergy and clinical immunology 107(5): 783-9	- Comparator in study does not match that specified in this review protocol *Study compared low-dose ICS/LABA to moderate-dose ICS - not a relevant comparison in this review*
McCarthy, TP, Greening, AP, Holgate, SK et al. (2001) The efficacy of salmeterol/fluticasone propionate combination (SFC) metered dose inhaler compared with beclomethasone dipropionate (BDP) in patients not well controlled at step 1 of the British guidelines on asthma management (BGAM). Thorax 56(suppl3): iii62	- Conference abstract
McCormack, P.L. and Lyseng-Williamson, K.A. (2007) Budesonide/formoterol: A review of its use as maintenance and reliever inhalation therapy in asthma. Drugs 67(16): 2407-2431	- Review article but not a systematic review
McKeage, Kate (2013) Fluticasone propionate/formoterol fumarate: a review of its use in persistent asthma. Drugs 73(2): 195-206	- No additional studies identified through reference checking
McKeage, Kate (2015) Tiotropium Respimat R: A Review of Its Use in Asthma Poorly Controlled with Inhaled Corticosteroids and Long-Acting beta2-Adrenergic Agonists. Drugs 75(7): 809-16	- Review article but not a systematic review
Meltzer, E O, Kuna, P, Nolte, H et al. (2012) Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function. The European respiratory journal 39(2): 279-89	- Population not relevant to this review protocol *Participants had to have asthma that was controlled in order to be enrolled*

Study	Code [Reason]
Meltzer, E., Casale, T., Shaikh, A. et al. (2018) ADD-ON TIOTROPIUM: CLINICAL IMPROVEMENT OF MODERATE ASTHMA REGARDLESS OF BASELINE IGE/EOSINOPHIL STATUS ACROSS AGE GROUPS. Annals of Allergy, Asthma and Immunology 121(5supplement): 42	- Conference abstract
Meltzer, E., Kuna, P., Nolte, H. et al. (2010) Effects of combined mometasone furoate and formoterol administered via a single metered-dose inhaler on moderate and severe asthma exacerbations as defined by the American Thoracic Society and the European Respiratory Society. Allergy: European Journal of Allergy and Clinical Immunology 65(suppl92): 538	- Conference abstract
Meltzer, E.; Nolte, H.; La Force, C. (2012) Efficacy and safety of combined mometasone furoate/ formoterol 100/10iG twice daily in subjects with asthma inadequately controlled on low-dose inhaled corticosteroids. World Allergy Organization Journal 5(suppl2): 80-s81	- Conference abstract
Meltzer, E., Shaikh, A., Engel, M. et al. (2017) Effect of tiotropium respimat 2.5 mug add-on to ICS or ICS+controller medications on clinical outcomes in adults and adolescents with asthma across severities. American Journal of Respiratory and Critical Care Medicine 195	- Conference abstract
Meltzer, E.O., Baena-Cagnani, C.E., Chervinsky, P. et al. (2007) Once-daily mometasone furoate administered by dry powder inhaler for the treatment of children with persistent asthma. Pediatric Asthma, Allergy and Immunology 20(2): 67-81	- Comparator in study does not match that specified in this review protocol *Study compared low-dose ICS to placebo - not a relevant comparison in this review protocol*
Meltzer, E.O., Nathan, R.A., Weinstein, S.F. et al. (2010) Low-, moderate-, and high-dose mometasone furoate/formoterol improves lung function in persistent asthmatics. Chest 138(4)	- Conference abstract
Meltzer, E.O.; Nolte, H.; LaForce, C. (2010) Treatment of moderate asthma with mometasone furoate and formoterol (MF/F) 100/10 mug twice-daily administered via a pressurized metered-dose inhaler: Efficacy and safety characteristics in subjects 12 years of age and older. American Journal of Respiratory and Critical Care Medicine 181(1meetingabstracts)	- Conference abstract

Study	Code [Reason]
Meltzer, Eli O, Lockey, Richard F, Friedman, Bruce F et al. (2002) Efficacy and safety of low-dose fluticasone propionate compared with montelukast for maintenance treatment of persistent asthma. Mayo Clinic proceedings 77(5): 437-45	- Population not relevant to this review protocol *Participants were not receiving ICS at baseline*
Meltzer, EO, Kalberg, C, Srebro, SH et al. (2001) Low dose fluticasone is more effective than montelukast for the treatment of persistent asthma. Annals of allergy, asthma & immunology 86: 82	- Comparator in study does not match that specified in this review protocol *Study compared low-dose fluticasone (220 mcg per day) plus montelukast with low-dose ICS/LABA combination (200/84 mcg fluticasone/salmeterol) - not a relevant comparator in this review*
Meltzer, EO; Nolte, H; LaForce, C (2010) Treatment Of Moderate Asthma With Mometasone Furoate And Formoterol (MF/F) 100/10 1/4g Twice-Daily Administered Via A Pressurized Metered-Dose Inhaler: efficacy And Safety Characteristics In Subjects 12 Years Of Age And Older. American journal of respiratory and critical care medicine 181(meetingabstracts): a5661	- Conference abstract
Meltzer, S.M., Spector, S.L., Uryniak, T. et al. (2011) Response to budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI) by patient's sex in non-black and black populations with asthma. Journal of Allergy and Clinical Immunology 127(2suppl1): ab160	- Conference abstract
Menezes, Marcelo B, Teixeira, Antonio L, Terra Filho, Joao et al. (2008) Inflammatory and functional effects of increasing asthma treatment with formoterol or double dose budesonide. Respiratory medicine 102(10): 1385-91	- Comparator in study does not match that specified in this review protocol *Study compares moderate dose ICS to low-dose ICS/LABA*
Miceli Sopo, S, Onesimo, R, Radzik, D et al. (2009) Montelukast versus inhaled corticosteroids as monotherapy for prevention of asthma: which one is best?. Allergologia et immunopathologia 37(1): 26-30	- No additional studies identified through reference checking
Miller, Christopher J; Senn, Stephen; Mezzanotte, William S (2008) Bronchodilation of formoterol administered with budesonide: device and formulation effects. Contemporary clinical trials 29(2): 114-24	- Inadequate study duration *Study treated participants with a single dose of therapy in a crossover design - inadequate duration to assess the outcomes listed in this protocol*

Study	Code [Reason]
Miller, David S, Yiu, Gloria, Hellriegel, Edward T et al. (2016) Dose-ranging study of salmeterol using a novel fluticasone propionate/salmeterol multidose dry powder inhaler in patients with persistent asthma. Allergy and asthma proceedings 37(4): 291-301	- No relevant outcomes identified *No outcomes reported in a time frame that was suitable for this review*
Miller, J. and Forbes, L. (2017) Randomized Trial of Once-Daily Fluticasone Furoate in Children with Inadequately Controlled Asthma. Pediatrics 140(supplement3): 219-s220	- Comparator in study does not match that specified in this review protocol *Study compared fluticasone propionate to fluticasone fuorate at varying doses - not a relevant comparator for this review*
Miraglia del Giudice, Michele, Piacentini, Giorgio L, Capasso, Michele et al. (2007) Formoterol, montelukast, and budesonide in asthmatic children: effect on lung function and exhaled nitric oxide. Respiratory medicine 101(8): 1809-13	- Inadequate study duration *Study treated participants for 4 weeks per therapy option - inadequate duration to assess the outcomes in this review protocol*
Miyamoto, T, Takahashi, T, Nakajima, S et al. (2001) Efficacy of budesonide Turbuhaler compared with that of beclomethasone dipropionate pMDI in Japanese patients with moderately persistent asthma. Respirology (Carlton, Vic.) 6(1): 27-35	- Inadequate study duration *Study provided treatment for 6 weeks - inadequate for outcomes listed in this review protocol*
Morgenstern-Kaplan, D. and Gonzalez-Estrada, A. (2022) Is the use of a combined FABA/ICS single inhaler for mild asthma effective and safe?. Clinical and Experimental Allergy 52(3): 372-374	- Included study details not provided
Moroni-Zentgraf, P., Vogelberg, C., Szefler, S.J. et al. (2017) Safety of tiotropium respimat add-on therapy in patients aged 6-17 years with symptomatic asthma. Respirology 22(supplement2): 106	- Conference abstract
Muiser, Susan, Gosens, Reinoud, van den Berge, Maarten et al. (2022) Understanding the role of long-acting muscarinic antagonists in asthma treatment. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 128(4): 352-360	- Review article but not a systematic review
Mukhopadhyay, Aniruddha, Waked, Mirna, Gogtay, Jaideep et al. (2020) Comparing the efficacy and safety of formoterol/budesonide pMDI versus its mono-components and other	- No additional studies identified through reference checking

Study	Code [Reason]
LABA/ICS in patients with asthma. Respiratory medicine 170: 106055	
Murphy, K., Bensch, G., Berger, W.E. et al. (2014) Once-daily tiotropium Respimatadd-on to inhaled corticosteroids +/- long-acting beta2-agonists improves lung function and asthma control and reduces risk of asthma worsening in patients with moderate or severe asthma. Annals of Allergy, Asthma and Immunology 113(5suppl1): a107	- Conference abstract
Murphy, K., Berger, W., Engel, M. et al. (2015) Tiotropium Respimat: Control in symptomatic asthma. Journal of General Internal Medicine 30(suppl2): 77	- Conference abstract
Murphy, K., Meltzer, E., Nathan, R. et al. (2012) Quality of life improvements in persistent asthma subjects receiving combined mometasone furoate and formoterol. World Allergy Organization Journal 5(suppl2): 80	- Conference abstract
Murphy, K., Meltzer, E., Weinstein, S. et al. (2012) Effects of mometasone furoate and formoterol fumarate combination therapy on 4 quality of life domains in patients with moderate asthma. Respirology 17(suppl2): 9	- Conference abstract
Murphy, K., Meltzer, E.O., Nathan, R.A. et al. (2010) Quality of life improvements in persistent asthma subjects receiving combined mometasone furoate and formoterol. Annals of Allergy, Asthma and Immunology 105(5): a51	- Conference abstract
Murphy, K.R., Meltzer, E.O., Nolte, H. et al. (2010) Quality of life is improved in persistent asthma subjects treated with mometasone furoate/formoterol: A new inhaled corticosteroid/long-acting beta2-agonist combination. Chest 138(4)	- Conference abstract
Murphy, K.R., Meltzer, E.O., Weinstein, S.F. et al. (2012) Effects of mometasone furoate and formoterol fumarate combinationtherapyon4quality of life domains in patients with moderateasthma. Annals of Allergy, Asthma and Immunology 109(suppl5): a55	- Conference abstract

Study	Code [Reason]
Murphy, Kevin R, Uryniak, Tom, Martin, Ubaldo J et al. (2012) The effect of budesonide/formoterol pressurized metered-dose inhaler on predefined criteria for worsening asthma in four different patient populations with asthma. Drugs in R&D 12(1): 9-14	- Secondary publication of an included study that does not provide any additional relevant information
Murphy, Kevin, Nelson, Harold, Parasuraman, Bhash et al. (2008) The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma. Current medical research and opinion 24(3): 879-94	- Study does not contain an intervention relevant to this review protocol *Study compares low-dose ICS/LABA (80/4.5 budesonide/formoterol, two inhalations twice daily) with low-dose ICS (80 mcg budesonide, two inhalations twice daily) - neither relevant to this review*
Murray, Clare S, Custovic, Adnan, Lowe, Lesley A et al. (2010) Effect of addition of salmeterol versus doubling the dose of fluticasone propionate on specific airway resistance in children with asthma. Allergy and asthma proceedings 31(5): 415-21	- Inadequate study duration *Study provided treatment for 6 weeks - inadequate for the outcomes in this review protocol*
Murray, J J, Church, N L, Anderson, W H et al. (1999) Concurrent use of salmeterol with inhaled corticosteroids is more effective than inhaled corticosteroid dose increases. Allergy and asthma proceedings 20(3): 173-80	- Comparator in study does not match that specified in this review protocol *Study compared low-dose ICS/LABA to moderate-dose ICS - not a relevant comparator in this review*
Nakamura, Yoichi, Hozawa, Soichiro, Sagara, Hironori et al. (2021) Efficacy and safety of once-daily, single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol in Japanese patients with inadequately controlled asthma: the CAPTAIN study. Current medical research and opinion 37(9): 1657-1665	- Secondary publication of an included study that does not provide any additional relevant information
Nathan BA, BREAKKYSRK, Nathan, BA, Boone, RI et al. (2000) Salmeterol and inhaled corticosteroids provide greater asthma control than montelukast and inhaled corticosteroids. Chest 118suppl4(4suppl): 85s	- Conference abstract
Nathan, R., Boulet, L.-P., Kerstjens, H. et al. (2020) CAPTAIN STUDY: EFFECT OF BASELINE LUNG FUNCTION ON RESPONSE TO TRIPLE THERAPY IN PATIENTS WITH ASTHMA INADEQUATELY CONTROLLED ON INHALED CORTICOSTEROID/LONG-ACTING BETA2-AGONIST THERAPY. Chest 158(4supplement): a2621-a2625	- Conference abstract

Study	Code [Reason]
Nathan, R., Nolte, H., Pearlman, D. et al. (2010) Effects of combined mometasone furoate and formoterol (200/10 mug BID) on the incidence of moderate and severe exacerbation in subjects with moderate asthma previously using moderate-dose inhaled corticosteroids. Allergy: European Journal of Allergy and Clinical Immunology 65(suppl92): 553	- Conference abstract
Nathan, R., Pearlman, D., Nayak, A. et al. (2009) Safety and tolerability of moderate-dose mometasone furoate/formoterol treatment versus mometasone furoate or formoterol monotherapies in persistent asthmatics who previously used moderate-dose inhaled corticosteroids (alone or with long-acting beta2-agonist). Chest 136(4)	- Conference abstract
Nathan, R., Pearlman, D., Nolte, H. et al. (2010) Efficacy and safety of combined moderate-dose mometasone furoate/Formoterol (MF/F) in persistent asthmatics. Journal of Allergy and Clinical Immunology 125(2suppl1): ab195	- Conference abstract
Nathan, R., Pearlman, D., Nolte, H. et al. (2009) Safety and tolerability of mometasone furoate/formoterol for persistent asthma subjects who previously were treated with moderate-dose inhaled corticosteroids (alone or with a long-acting beta2-agonist). Annals of Allergy, Asthma and Immunology 103(5suppl3): a58	- Conference abstract
Nathan, R., Weinstein, S., Meltzer, E. et al. (2009) Safety of mometasone furoate/formoterol combination therapy for the treatment of persistent asthma. Annals of Allergy, Asthma and Immunology 103(5suppl3): a66	- Conference abstract
Nathan, R.A.; Meltzer, E.O.; Nolte, H. (2010) The effect of mometasone furoate/formoterol combination treatment on severe exacerbations requiring hospitalization, emergency treatment, or systemic corticosteroid treatment: Results from two randomized, placebo-controlled studies. Chest 138(4)	- Conference abstract
Nathan, R.A., Pearlman, D., Nolte, H. et al. (2010) Efficacy and safety of mometasone furoate and formoterol (MF/F) 200/10 mug twice-daily administered via a pressurized metered-dose inhaler in subjects 12 years of age and older with moderate-to-severe asthma.	- Conference abstract

Study	Code [Reason]
American Journal of Respiratory and Critical Care Medicine 181(1meetingabstracts)	
Nathan, R.A., Pearlman, D.S., Nolte, H. et al. (2010) Efficacy and safety of combined moderate-dose mometasone furoate/formoterol (MF/F) in persistent asthmatics. Allergy, Asthma and Clinical Immunology 6(suppl2)	- Conference abstract
Nathan, Robert A, Nolte, Hendrik, Pearlman, David S et al. (2010) Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg combination treatment in patients with persistent asthma previously receiving moderate-dose inhaled corticosteroids. Allergy and asthma proceedings 31(4): 269-79	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Nathan, Robert A, Rooklin, Anthony, Schoaf, Lynne et al. (2006) Efficacy and tolerability of fluticasone propionate/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescent and adult patients with persistent asthma: a randomized, double-blind, placebo-controlled, 12-week study. Clinical therapeutics 28(1): 73-85	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Nayak, A., LaForce, C., Nathan, R.A. et al. (2010) Mometasone furoate/formoterol administered via a pressurized metered-dose inhaler improves proportions of saba-free days and nights in subjects with persistent asthma. Annals of Allergy, Asthma and Immunology 105(5): a50-a51	- Conference abstract
Nayak, A.S., Nathan, R.A., Meltzer, E.O. et al. (2011) Mometasone furoate/formoterol combination therapy increases frequency of days/nights free of short-acting beta2-agonist use. Journal of Allergy and Clinical Immunology 127(2suppl1): ab86	- Conference abstract
Nelson, H S, Busse, W W, Kerwin, E et al. (2000) Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. The Journal of allergy and clinical immunology 106(6): 1088-95	- Comparator in study does not match that specified in this review protocol *Study compared low dose ICS (200 mcg fluticasone per day) plus montelukast with low-dose ICS/LABA (100/50 fluticasone/salmeterol twice daily) - not a relevant comparator in this review*
Nelson, Harold S, Chapman, Kenneth R, Pyke, Stephen D et al. (2003) Enhanced synergy	- Comparator in study does not match that specified in this review protocol

Study	Code [Reason]
between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. The Journal of allergy and clinical immunology 112(1): 29-36	*Review compares combination and concurrent ICS/LABA - not relevant to this review protocol*
Ng, D.K.K., Chan, C.H., Wu, S. et al. (2007) Oral montelukast versus inhaled budesonide in children with mild persistent asthma: A pilot study. Hong Kong Journal of Paediatrics 12(1): 3	- Conference abstract
Nolte, H.; Maspero, J.; Ojeda, I.C. (2009) The safety and tolerability characteristics of mometasone furoate/formoterol combination therapy in patients with persistent asthma: Findings from the phase III clinical development program. Chest 136(4)	- Conference abstract
Nolte, H., Nathan, R.A., Meltzer, E.O. et al. (2010) Mometasone furoate/formoterol combination therapy reduces nocturnal awakenings in patients with moderate or severe asthma. Chest 138(4)	- Conference abstract
Noonan, M J, Chervinsky, P, Brandon, M et al. (1998) Montelukast, a potent leukotriene receptor antagonist, causes dose-related improvements in chronic asthma. Montelukast Asthma Study Group. The European respiratory journal 11(6): 1232-9	- Study does not contain an intervention relevant to this review protocol *Montelukast as a sole therapy not a treatment option in this review for adults*
Norhaya, M R; Yap, T M; Zainudin, B M (1999) Addition of inhaled salmeterol to inhaled corticosteroids in patients with poorly controlled nocturnal asthma. Respirology (Carlton, Vic.) 4(1): 77-81	- Study does not contain an intervention relevant to this review protocol *Study allowed participants to continue using maintenance therapy including sodium cromoglycate and theophylline which were not specified in this review protocol*
Nsouli, S. (2017) Efficacy of inhaled tiotropium for asthmatics uncontrolled using inhaled corticosteroid plus a long-acting beta2-agonist. Annals of Allergy, Asthma and Immunology 119(5supplement1): 53	- Conference abstract
Nsouli, S. (2010) The addition of formoterol a long acting inhaled beta 2-adrenergic receptor agonist to a low dose inhaled corticosteroid compared with a double dose of an inhaled corticosteroid in patients with persistent asthma. Annals of Allergy, Asthma and Immunology 105(5): a43-a44	- Conference abstract

Study	Code [Reason]
Nsouli, SM and McNutt, WJ (2001) The additive effects of montelukast and salmeterol in moderate asthmatics who are uncontrolled on a low dose on inhaled corticosteroids. Annals of allergy, asthma & immunology 86: 81	- Conference abstract
Nsouli, SM and McNutt, WJ (2000) The addition of montelukast to a low dose inhaled corticosteroid compared with a doubl-dose of an inhaled corticosteroid in patients with persistent asthma. Annals of allergy, asthma & immunology 84: 159	- Conference abstract
O'Byrne, P M, Barnes, P J, Rodriguez-Roisin, R et al. (2001) Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. American journal of respiratory and critical care medicine 164(8pt1): 1392-7	- Data not reported in an extractable format or a format that can be analysed
O'Byrne, Paul M, Naya, Ian P, Kallen, Anders et al. (2008) Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled beta2-agonists in achieving asthma control. Chest 134(6): 1192-1199	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
O'Connor, Richard D, Patrick, Donald L, Parasuraman, Bhash et al. (2010) Comparison of patient-reported outcomes during treatment with adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler versus fixed-dose fluticasone propionate/salmeterol dry powder inhaler in patients with asthma. The Journal of asthma : official journal of the Association for the Care of Asthma 47(2): 217-23	- Comparator in study does not match that specified in this review protocol *Study compared two doses of ICS/LABA - not a relevant comparison in this review*
O'Dowd, L, Berger, WE, Leflein, JG et al. (2008) Health-related quality of life (HRQL) and asthma control after long-term treatment with budesonide and formoterol administered via one pressurized metered-dose inhaler (pMDI) compared with budesonide dry powder inhaler (DPI) alone in children with asthma. Journal of allergy and clinical immunology 121(2suppl1): 152	- Conference abstract
O'Sullivan, Siobhan, Akveld, Martijn, Burke, Conor M et al. (2003) Effect of the addition of montelukast to inhaled fluticasone propionate on airway inflammation. American journal of respiratory and critical care medicine 167(5): 745-50	- Comparator in study does not match that specified in this review protocol *Study compared regular ICS to ICS + montelukast - not a relevant intervention in this population*

Study	Code [Reason]
Oba, Y., Patel, T., Anwer, S. et al. (2020) Addition of long-acting beta2 agonists or long-acting muscarinic antagonists versus doubling the dose of inhaled corticosteroids (ICS) in adolescents and adults with uncontrolled asthma with moderate dose ICS: a systematic review and network meta-analysis. Cochrane Database of Systematic Reviews 2020(11): cd013797	- study protocol
Oba, Yuji, Anwer, Sumayya, Maduke, Tinashe et al. (2022) Effectiveness and tolerability of dual and triple combination inhaler therapies compared with each other and varying doses of inhaled corticosteroids in adolescents and adults with asthma: a systematic review and network meta-analysis. The Cochrane database of systematic reviews 12: cd013799	- No relevant studies identified from included studies
Ohta, K., Ichinose, M., Tohda, Y. et al. (2014) Once-daily tiotropium respimat is well tolerated and efficacious over 52 weeks in japanese patients with symptomatic asthma receiving inhaled corticosteroids (ICS) +/- long-acting beta2-agonist (LABA): A randomized, double-blind, placebo-controlled study. American Journal of Respiratory and Critical Care Medicine 189(meetingabstracts)	- Conference abstract
Ohta, Ken, Ichinose, Masakazu, Tohda, Yuji et al. (2015) Long-Term Once-Daily Tiotropium Respimat R Is Well Tolerated and Maintains Efficacy over 52 Weeks in Patients with Symptomatic Asthma in Japan: A Randomised, Placebo-Controlled Study. PloS one 10(4): e0124109	- Comparator in study does not match that specified in this review protocol *Study compared adding LAMA to current therapy vs maintaining current therapy with a placebo - not a relevant comparator in this review*
Ojanguren, Inigo and Pilia, Maria Florencia (2021) Efficacy and safety of once-daily single-inhaler triple therapy in patients with inadequately controlled asthma: the CAPTAIN trial. Breathe (Sheffield, England) 17(1): 200279	- Not a peer-reviewed publication
Oliver, Amanda J, Covar, Ronina A, Goldfrad, Caroline H et al. (2016) Randomized Trial of Once-Daily Fluticasone Furoate in Children with Inadequately Controlled Asthma. The Journal of pediatrics 178: 246-253e2	- Study does not contain an intervention relevant to this review protocol *Study compares between ICS doses - not a relevant comparison in this review*
Oliver, Amanda, Allen, Ann, VanBuren, Sandi et al. (2014) Safety, tolerability, pharmacokinetics, and pharmacodynamics of fluticasone furoate, a novel inhaled corticosteroid, in children aged 5-	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*

Study	Code [Reason]
11 years with persistent asthma: A randomized trial. Clinical pharmacology in drug development 3(2): 144-50	
Oliver, Amanda, VanBuren, Sandi, Allen, Ann et al. (2014) Tolerability of fluticasone furoate/vilanterol combination therapy in children aged 5 to 11 years with persistent asthma. Clinical therapeutics 36(6): 928-939e1	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Oppenheimer, J., Abott, C., Chang, S. et al. (2021) CAPTAIN STUDY: EFFECTS OF BASELINE IGE LEVELS ON TRIPLE THERAPY RESPONSE IN INADEQUATELY CONTROLLED ASTHMA. Annals of Allergy, Asthma and Immunology 127(5supplement): 14	- Conference abstract
Oppenheimer, J., Brusselle, G., Busse, W. et al. (2020) CAPTAIN STUDY: TREATMENT OUTCOMES FROM FLUTICASONE FUROATE/UMECLIDINIUM/VILANTEROL ACCORDING TO HISTORY OF SEVERE ASTHMA EXACERBATIONS. Annals of Allergy, Asthma and Immunology 125(5supplement): 26-s27	- Conference abstract
Ortega, V.E., Daya, M., Szefler, S.J. et al. (2021) Pharmacogenetic studies of long-acting beta agonist and inhaled corticosteroid responsiveness in randomised controlled trials of individuals of African descent with asthma. The Lancet Child and Adolescent Health 5(12): 862-872	- No relevant outcomes identified
Ortega-Cisneros, M, Maldonado-Alaniz, ML, RosasVargas, MA et al. (1998) Salmeterol and inhaled beclomethasone versus high dose inhaled beclomethasone in the control of pediatric patients with moderate asthma. Annals of allergy, asthma and immunology 80: 131	- Conference abstract
Ostrom, Nancy K, Decotiis, Bruce A, Lincourt, William R et al. (2005) Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. The Journal of pediatrics 147(2): 213-20	- Population not relevant to this review protocol *Participants could have received additional medication other than ICS and bronchodilators prior to inclusion*
Paggiaro, P., Corradi, M., Raptis, H. et al. (2014) High dose extrafine beclomethasone/formoterol via metered dose inhaler is effective and safe in asthmatics not controlled on moderate-high dose of inhaled	- Conference abstract

Study	Code [Reason]
corticosteroids. European Respiratory Journal 44(suppl58)	
Paggiaro, P., Engel, M., Tudoric, N. et al. (2013) Phase III trial of tiotropium as add-on therapy to low-dose inhaled corticosteroids for patients with symptomatic mild persistent asthma: Design and planned analyses. European Respiratory Journal 42(suppl57)	- Conference abstract
Paggiaro, P., Halpin, D.M.G., Buhl, R. et al. (2014) Tiotropium Respimat add-on to inhaled corticosteroids improves lung function in patients with symptomatic mild asthma: Results from a phase III trial. Thorax 69(suppl2): a191	- Conference abstract
Paggiaro, P., Kuna, P., Kots, M. et al. (2019) Efficacy and safety of a fixed combination extrafine beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) PMDI treatment compared to fixed combination BDP/FF in patients with uncontrolled asthma on moderate dose ICS/LABA: The trimaran study. American Journal of Respiratory and Critical Care Medicine 199(9)	- Conference abstract
Paggiaro, P; Nicolini, G; Papi, A (2008) Extrafine beclomethasone dipropionate/formoterol hydrofluoroalkane-propelled inhaler in asthma. Expert review of respiratory medicine 2(2): 161-166	- Review article but not a systematic review
Paggiaro, Pierluigi, Halpin, David M G, Buhl, Roland et al. (2016) The Effect of Tiotropium in Symptomatic Asthma Despite Low- to Moderate-Dose Inhaled Corticosteroids: A Randomized Controlled Trial. The journal of allergy and clinical immunology. In practice 4(1): 104-13e2	- Comparator in study does not match that specified in this review protocol *Study compared adding LAMA to current therapy vs maintaining current therapy with a placebo - not a relevant comparator in this review*
Papi, A., Barnes, N., Fowler, A. et al. (2021) CAPTAIN: Effects of lung function at screening (FEV1 % predicted) as a continuous variable on treatment outcomes. European Respiratory Journal 58(suppl65)	- Conference abstract
Papi, A., Chipps, B.E., Beasley, R.W. et al. (2022) Efficacy and Safety of As-Needed Albuterol/Budesonide versus As- Needed Albuterol in Adults, Adolescents, and Children Aged >=4 Years with Moderate-to-Severe Asthma: Results of the MANDALA Study.	- Conference abstract

Study	Code [Reason]
American Journal of Respiratory and Critical Care Medicine 205(1)	
Papi, A., Lee, L., Kerstjens, H. et al. (2020) CAPTAIN: Effects of smoking status on response to triple therapy in patients with inadequately controlled asthma on ICS/LABA. European Respiratory Journal 56(supplement64)	- Conference abstract
Papi, A., Lee, L., Kerstjens, H.A. et al. (2022) CAPTAIN Study: Effects of smoking status on treatment response to triple therapy in patients with inadequately controlled asthma on inhaled corticosteroid/long-acting b2-agonist (ICS/LABA) therapy. Allergy and Asthma Proceedings 43(1): 88-89	- Conference abstract
Papi, A., Price, D., Sastre, J. et al. (2013) Fluticasone propionate/formoterol fumarate improves asthma control and reduces exacerbations compared with fluticasone. European Respiratory Journal 42(suppl57)	- Conference abstract
Papi, A., Price, D., Sastre, J. et al. (2013) Fluticasone propionate/formoterol fumarate improves asthma control and reduces exacerbations compared with fluticasone. Respirology 18(suppl4): 112	- Conference abstract
Papi, A., Singh, D., Virchow, C.J. et al. (2020) Effect of triple therapy with extra-fine BDP/FF/GB pMDI during seasonal peaks of asthma exacerbations. A post-hoc analysis of the TRIMARAN and TRIGGER studies. European Respiratory Journal 56(supplement64)	- Conference abstract
Papi, A, Nicolini, G, Baraldi, E et al. (2009) Regular vs prn nebulized treatment in wheeze preschool children. Allergy 64(10): 1463-1471	- Study does not contain an intervention relevant to this review protocol *Study compared as-needed combination inhaler to regular ICS and SABA as-needed - included in 3.1*
Papi, A, Paggiaro, P L, Nicolini, G et al. (2007) Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma. The European respiratory journal 29(4): 682-9	- Comparator in study does not match that specified in this review protocol *Study compared two ICS/LABA combinations (beclomethasone/formoterol vs budesonide/formoterol) - within-drug class comparisons are not relevant to this review*

Study	Code [Reason]
Papi, A, Paggiaro, P, Nicolini, G et al. (2007) Beclomethasone/formoterol vs fluticasone/salmeterol inhaled combination in moderate to severe asthma. Allergy 62(10): 1182-8	- Comparator in study does not match that specified in this review protocol *Study compared two ICS/LABA combination therapies (beclomethasone/formoterol vs fluticasone/salmeterol) - within-drug class comparisons not relevant to this review*
Papi, A, Singh, D, Virchow, JC et al. (2022) Normalisation of airflow limitation in asthma: post-hoc analyses of TRIMARAN and TRIGGER. Clinical and translational allergy 12(4)	- Secondary publication of an included study that does not provide any additional relevant information
Papi, A, Virchow, JC, Singh, D et al. (2021) Extrafine triple therapy and asthma exacerbation seasonality: TRIMARAN and TRIGGER post hoc analyses. Journal of allergy and clinical immunology 148(1): 262-265.e2	- Secondary publication of an included study that does not provide any additional relevant information
Papi, Alberto, Canonica, Giorgio W, Maestrelli, Piero et al. (2007) Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. The New England journal of medicine 356(20): 2040-52	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Papi, Alberto, Chipps, Bradley E, Beasley, Richard et al. (2022) Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma. The New England journal of medicine 386(22): 2071-2083	- Comparator in study does not match that specified in this review protocol *SABA alone was the comparator - not relevant to this review*
Papi, Alberto, Corradi, Massimo, Pigeon-Francisco, Catherine et al. (2013) Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. The Lancet. Respiratory medicine 1(1): 23-31	- Comparator in study does not match that specified in this review protocol *Study compared low-dose regular ICS/formoterol plus as-needed ICS/formoterol to regular low-dose ICS/LABA (100/6 mcg beclomethasone/formoterol twice daily) - low-dose ICS/LABA is not a relevant intervention in this review*
Papi, Alberto, Marku, Brunilda, Scichilone, Nicola et al. (2015) Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. The Lancet. Respiratory medicine 3(2): 109-119	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Papi, Alberto, Price, David, Sastre, Joaquin et al. (2015) Efficacy of fluticasone propionate/formoterol fumarate in the treatment	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
of asthma: a pooled analysis. Respiratory medicine 109(2): 208-17	*Secondary analysis of studies including interventions that are not relevant to this review*
Papi, Alberto, Qasuri, Murtaza, Chung, Ernestine et al. (2023) Fixed-dose combination fluticasone/formoterol for asthma treatment in a real-world setting: meta-analysis of exacerbation rates and asthma control. European clinical respiratory journal 10(1): 2174642	- Study design not relevant to this review protocol *Systematic review of non-randomised trials*
Patel, M., Pilcher, J., Shaw, D. et al. (2013) Maintenance and reliever combination budesonide/formoterol therapy in asthma patients at risk of severe exacerbations: A randomised controlled trial. European Respiratory Journal 42(suppl57)	- Conference abstract
Patel, M., Pilcher, J., Shaw, D. et al. (2013) A randomised controlled trial of single combination budesonide/formoterol inhaler as maintenance and reliever therapy in asthma patients at risk of severe exacerbations. Thorax 68(suppl3): a148	- Conference abstract
Pauwels, R A, Lofdahl, C G, Postma, D S et al. (1997) Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. The New England journal of medicine 337(20): 1405-11	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Pauwels, R.A., Lofdahl, C.-G., Postma, D.S. et al. (1997) Effect of inhaled formoterol and budesonide on exacerbations of asthma. New England Journal of Medicine 337(20): 1405-1411	- Duplicate reference
Pauwels, R, Smiltena, I, Bagdonas, A et al. (2004) Seretide 50/100 once daily is more effective than budesonide 400mcg once daily in mild asthma. American journal of respiratory and critical care medicine 169(7): a86	- Conference abstract
Pavord, I., Peachey, G., Kerstjens, H. et al. (2020) Once-daily, single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI in inadequately controlled asthma: the CAPTAIN study. Journal of Allergy and Clinical Immunology 145(2supplement): ab241	- Conference abstract

Study	Code [Reason]
Pavord, I., Peachey, G., Kerstjens, H. et al. (2020) Once-daily, single-inhaler fluticasone furoate/umeclidi- nium/VIlanterol (ff/umec/VI) versus ff/VI in inadequately controlled asthma: The captain study. Allergy and Asthma Proceedings 41(6): 459-460	- Conference abstract
Pavord, I.D., Fowler, A., Kerstjens, H. et al. (2020) Captain study: Treatable traits and the outcome of treatment with inhaled fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI therapies in patients with uncontrolled asthma, a pre-specified subgroup analysis. American Journal of Respiratory and Critical Care Medicine 201(1)	- Conference abstract
Pavord, Ian D, Holliday, Mark, Reddel, Helen K et al. (2020) Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. The Lancet. Respiratory medicine 8(7): 671-680	- Study does not contain an intervention relevant to this review protocol *As needed ICS/LABA not a relevant intervention in this review*
Pearlman, D., Nathan, R., Meltzer, E. et al. (2010) Effect of mometasone furoate/formoterol (MF/F) combination therapy on nocturnal awakenings in subjects with persistent asthma. Journal of Allergy and Clinical Immunology 125(2suppl1): ab194	- Conference abstract
Pearlman, D.S.; La-Force, C.; Kaiser, K. (2011) Fluticasone propionate/formoterol fumarate combination therapy has superior efficacy to both fluticasone and formoterol alone. European Respiratory Journal 38(suppl55)	- Conference abstract
Pearlman, David, Qaqundah, Paul, Matz, Jonathan et al. (2009) Fluticasone propionate/salmeterol and exercise-induced asthma in children with persistent asthma. Pediatric pulmonology 44(5): 429-35	- Inadequate study duration *Study treated participants for 4 weeks - inadequate duration to assess the outcomes listed in this review protocol*
Pedersen, Soren E, Bateman, Eric D, Bousquet, Jean et al. (2007) Determinants of response to fluticasone propionate and salmeterol/fluticasone propionate combination in the Gaining Optimal Asthma controL study. The Journal of allergy and clinical immunology 120(5): 1036-42	- Secondary publication of an included study that does not provide any additional relevant information

Study	Code [Reason]
Pedersen, Soren, Maspero, Jorge, Gul, Nadeem et al. (2011) Components of asthma control and treatment response of individual control criteria in children: analysis of the PEACE study. Pediatric pulmonology 46(12): 1182-8	- Secondary publication of an included study that does not provide any additional relevant information
Pelaia, Corrado, Crimi, Claudia, Crimi, Nunzio et al. (2022) Indacaterol/glycopyrronium/mometasone fixed dose combination for uncontrolled asthma. Expert review of respiratory medicine 16(2): 183-195	- Review article but not a systematic review
Pertseva, T.; Dissanayake, S.; Kaiser, K. (2012) Efficacy and safety of fluticasone/formoterol compared to fluticasone alone in patients with asthma. European Respiratory Journal 40(suppl56)	- Conference abstract
Peters, S.P. (2011) Tiotropium plus beclomethasone was more effective than doubling beclomethasone for asthma. Annals of Internal Medicine 154(4): jc2-4	- Not a peer-reviewed publication
Peters, Stephen P, Bleecker, Eugene R, Canonica, Giorgio W et al. (2016) Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone. The New England journal of medicine 375(9): 850-60	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Peters, Stephen P, Bleecker, Eugene R, Kunselman, Susan J et al. (2013) Predictors of response to tiotropium versus salmeterol in asthmatic adults. The Journal of allergy and clinical immunology 132(5): 1068-1074e1	- Population not relevant to this review protocol *Secondary analysis of Peters (2010) - participants had received therapies other that ICS and bronchodilators at screening*
Peters, Stephen P, Kunselman, Susan J, Icitovic, Nikolina et al. (2010) Tiotropium bromide step-up therapy for adults with uncontrolled asthma. The New England journal of medicine 363(18): 1715-26	- Population not relevant to this review protocol *Participants had received therapies other than ICS and bronchodilators prior to study entry (43% LTRA, 25% theophylline, 24% anticholinergics)*
Pijaskic Kamenov, SS, Filipovic, MD, Kamenov, BA et al. (2001) Sustained release theophylline added to fluticasone propionate in the treatment of paediatric asthma. European respiratory journal 18(suppl33): 123s	- Conference abstract
Pilcher, J., Patel, M., Smith, A. et al. (2013) Single budesonide/formoterol inhaler as	- Conference abstract

Study	Code [Reason]
maintenance and reliever therapy is beneficial in maori asthma. Respirology 18(suppl2): 44	
Pilcher, J., Patel, M., Smith, A. et al. (2013) The budesonide/formoterol inhaler as maintenance and reliever therapy in Maori asthmatics. European Respiratory Journal 42(suppl57)	- Conference abstract
Pilcher, Janine, Patel, Mitesh, Pritchard, Alison et al. (2017) Beta-agonist overuse and delay in obtaining medical review in high risk asthma: a secondary analysis of data from a randomised controlled trial. NPJ primary care respiratory medicine 27(1): 33	- Secondary publication of an included study that does not provide any additional relevant information
Pilcher, Janine, Patel, Mitesh, Reddel, Helen K et al. (2016) Effect of smoking status on the efficacy of the SMART regimen in high risk asthma. Respirology (Carlton, Vic.) 21(5): 858-66	- Secondary publication of an included study that does not provide any additional relevant information
Pilcher, Janine, Patel, Mitesh, Smith, Ann et al. (2014) Combination budesonide/formoterol inhaler as maintenance and reliever therapy in Maori with asthma. Respirology (Carlton, Vic.) 19(6): 842-51	- Secondary publication of an included study that does not provide any additional relevant information
Pizzichini, M.M., Stirbulov, R., Fristcher, C.C. et al. (2012) Efficacy and safety of a combination of budesonide/formoterol in a single capsule in uncontrolled asthma. American Journal of Respiratory and Critical Care Medicine 185(meetingabstracts)	- Conference abstract
Pljaskic-Kamenov, SS; Filipovic, MD; Kamenov, BA (2000) Comparison of addition of salmeterol xinafoate to budesonide wiwth budesonide alone on symptoms and quality of life in asthmatic children. European respiratory journal 16(suppl31): 518s	- Conference abstract
Ploszczuk, Anna, Bosheva, Miroslava, Spooner, Kay et al. (2018) Efficacy and safety of fluticasone propionate/formoterol fumarate in pediatric asthma patients: a randomized controlled trial. Therapeutic advances in respiratory disease 12: 1753466618777924	- Comparator in study does not match that specified in this review protocol *Study compared low-dose ICS/LABA (50/100 salmeterol/fluticasone twice daily) to low-dose ICS (100 mcg fluticasone twice daily) - low-dose ICS is not a relevant intervention in this review*
Pohl, W R, Vetter, N, Zwick, H et al. (2006) Adjustable maintenance dosing with budesonide/formoterol or budesonide: double-	- Population not relevant to this review protocol

Study	Code [Reason]
blind study. Respiratory medicine 100(3): 551-60	*Participants could have received additional medication other than ICS and bronchodilators prior to inclusion*
Pohunek, Petr, Kuna, Piotr, Jorup, Carin et al. (2006) Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 17(6): 458-65	- Inadequate study duration *No outcomes reported that are relevant within the timeframe of the study*
Postma, Dirkje S; O'Byrne, Paul M; Pedersen, Soren (2011) Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control. Chest 139(2): 311-318	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Price, D., Bateman, E.D., Paggiaro, P. et al. (2014) Efficacy of once-daily tiotropium respimat 5 mug from five phase III trials in adults with symptomatic asthma. Thorax 69(suppl2): a50	- Conference abstract
Price, D., Engel, M., Moroni-Zentgraf, P. et al. (2014) Once-daily tiotropium respimat add-on to ICS + LABA improves symptom control and reduces exacerbations in patients with symptomatic asthma. Thorax 69(suppl2): a49-a50	- Conference abstract
Price, D., Papi, A., Kaiser, K. et al. (2011) Fluticasone propionate/formoterol fumarate combination therapy is more efficacious in improving lung function than its individual components in patients with asthma. Thorax 66(suppl4): a112	- Conference abstract
Price, D., Papi, A., Tamm, M. et al. (2011) Fluticasone propionate/formoterol fumarate combination therapy is superior to fluticasone propionate alone in improving asthma control. Thorax 66(suppl4): a113	- Conference abstract
Price, D, Dutchman, D, Mawson, A et al. (2002) Early asthma control and maintenance with eformoterol following reduction of inhaled corticosteroid dose. Thorax 57(9): 791-8	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Price, DB, Hernandez, D, Magyar, P et al. (2002) Adding montelukast is at least as efficacious as doubling the budesonide dose in	- Conference abstract

Study	Code [Reason]
persistent asthma: results of the compact study. American journal of respiratory and critical care medicine 165(suppl8): a216	
Priestley, A., Woodward, J., McIver, T. et al. (2011) Effect of high dose inhaled fluticasone/ formoterol combination therapy compared with its separate components on the hypothalamo-pituitary-adrenal (HPA) axis function. Allergy: European Journal of Allergy and Clinical Immunology 66(suppl94): 586	- Conference abstract
Prosser, Theresa R and Bollmeier, Suzanne G (2015) Fluticasone-formoterol: a systematic review of its potential role in the treatment of asthma. Therapeutics and clinical risk management 11: 889-99	- No additional studies identified through reference checking
Quirce, Santiago, Barcina, Carlos, Plaza, Vicente et al. (2011) A comparison of budesonide/formoterol maintenance and reliever therapy versus conventional best practice in asthma management in Spain. The Journal of asthma : official journal of the Association for the Care of Asthma 48(8): 839-47	- Comparator in study does not match that specified in this review protocol *Study compared regular ICS/formoterol plus as-needed to conventional best practice - not a relevant comparator in this review*
Rabinovitch, Nathan, Mauger, David T, Reisdorph, Nichole et al. (2014) Predictors of asthma control and lung function responsiveness to step 3 therapy in children with uncontrolled asthma. The Journal of allergy and clinical immunology 133(2): 350-6	- Secondary publication of an included study that does not provide any additional relevant information
Radwan, Z.M., Yamamah, G.A.N., Shaaban, H.H. et al. (2010) Effect of different monotherapies on serum nitric oxide and pulmonary functions in children with mild persistent asthma. Archives of Medical Science 6(6): 919-925	- Inadequate study duration
Raherison-Semjen, C., Singh, D., Kerstjens, H.A.M. et al. (2021) Mometasone/ indacaterol/ glycopyrronium demonstrates similar efficacy in men and women: post hoc analysis of IRIDIUM study. European Respiratory Journal 58(suppl65)	- Conference abstract
Rajanandh, M.G., Ahalya, S.P., Anjali, R. et al. (2019) A systematic review of second-line controller combination therapy options for the management of asthma. Drugs and Therapy Perspectives 35(2): 77-85	- No additional studies identified through reference checking

Study	Code [Reason]
Rajanandh, Muhasaparur Ganesan; Nageswari, Arcot D; Ilango, Kaliappan (2015) Assessment of montelukast, doxofylline, and tiotropium with budesonide for the treatment of asthma: which is the best among the second-line treatment? A randomized trial. Clinical therapeutics 37(2): 418-26	- Comparator in study does not match that specified in this review protocol *Study compared low-dose ICS/LABA to low-dose ICS with montelukast or LAMA - not relevant comparators in this population (3.2a)*
Rajanandh, Muhasaparur Ganesan; Nageswari, Arcot Deenadayalu; Ilango, Kaliappan (2014) Assessment of various second-line medications in addition to inhaled corticosteroid in asthma patients: a randomized controlled trial. Clinical and experimental pharmacology & physiology 41(7): 509-13	- Population not relevant to this review protocol *Unclear if participants had asthma that was uncontrolled - inadequate methodology description to assess*
Raphael, G., Yiu, G., Sakov, A. et al. (2017) Patient-reported outcomes and quality of life improved with fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers versus placebo in patients with persistent asthma. Journal of Allergy and Clinical Immunology 139(2supplement1): ab10	- Conference abstract
Raphael, Gordon, Yiu, Gloria, Sakov, Anat et al. (2018) Randomized, double-blind trial evaluating the efficacy and safety of fluticasone propionate and fluticasone propionate/salmeterol delivered via multidose dry powder inhalers in patients with persistent asthma aged 12 years and older. The Journal of asthma : official journal of the Association for the Care of Asthma 55(6): 640-650	- Study does not contain an intervention relevant to this review protocol *Study compared low-dose ICS (50 or 100 mcg fluticasone propionate twice daily) to low-dose ICS/LABA (50/12.5 or 100/12.5 fluticasone/salmeterol) - low-dose ICS and ICS combinations are not relevant interventions in this review*
Reddel, H., Bateman, E., FitzGerald, J. et al. (2021) As-needed budesonide-formoterol efficacy and safety in adolescents with mild asthma. Respirology 26(suppl2): 76	- Conference abstract
Reddel, H., Bateman, E., Fitzgerald, J. et al. (2020) As-Needed Budesonide/Formoterol for Adolescents Was Superior to As-Needed Terbutaline and Comparable to Budesonide Maintenance for Severe Exacerbation Risk Reduction: Pooled Subgroup Analysis of the Sygma 1 and 2 Trials. Respirology 25: 97	- Conference abstract
Reddel, H., O'Byrne, P., Bateman, E. et al. (2021) NNT to prevent one exacerbation with as-needed budesonide-formoterol. Respirology 26(suppl2): 81	- Conference abstract

Study	Code [Reason]
Reddel, H., OaByrne, P., D Bateman, E. et al. (2020) Number Needed to Treat with As-Needed Budesonide/Formoterol or Budesonide Maintenance to Have An Additional Patient Free from A Severe or Moderate/Severe Exacerbation: Post-Hoc Analysis of Sygma 1 in Mild Asthma. Respirology 25: 106	- Conference abstract
Reddel, Helen K, O'Byrne, Paul M, FitzGerald, J Mark et al. (2021) Efficacy and Safety of As-Needed Budesonide-Formoterol in Adolescents with Mild Asthma. The journal of allergy and clinical immunology. In practice 9(8): 3069-3077e6	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Reddel, Helen Kathryn, Brusselle, Guy, Lamarca, Rosa et al. (2023) Safety and Effectiveness of As-Needed Formoterol in Asthma Patients Taking Inhaled Corticosteroid (ICS)-Formoterol or ICS-Salmeterol Maintenance Therapy. The journal of allergy and clinical immunology. In practice 11(7): 2104-2114e3	- Study does not contain an intervention relevant to this review protocol *Study compared formoterol and salbutamol as reliever medications*
Rely, K., Gonzalez, S.E., Alexandre, P.K. et al. (2010) Cost-effectiveness of salmeterol/fluticasone propionate combination versus leukotriene montelukast for the control of persistent asthma in children. Value in Health 13(7): a323-a324	- Conference abstract
Riccioni, G., Ballone, E., D'Orazio, N. et al. (2002) Effectiveness of montelukast versus budesonide on quality of life and bronchial reactivity in subjects with mild-persistent asthma. International journal of immunopathology and pharmacology 15(2): 149-155	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Richter, K, Hartmann, U, Metzenauer, P et al. (2007) Randomised trial comparing as-needed versus regular treatment with formoterol in patients with persistent asthma. Respiratory medicine 101(3): 467-75	- Comparator in study does not match that specified in this review protocol *Study compared ICS + regular formoterol to ICS + formoterol as-needed - not a relevant comparator in this review*
Rickard, K, Goode Sellers, S, Edwards, L et al. (2001) Low-dose fluticasone is superior to montelukast in asthma patients. European respiratory journal 18(suppl33): 262s	- Conference abstract

Study	Code [Reason]
Riemersma, Roland A; Postma, Dirkje; van der Molen, Thys (2012) Budesonide/formoterol maintenance and reliever therapy in primary care asthma management: effects on bronchial hyperresponsiveness and asthma control. Primary care respiratory journal : journal of the General Practice Airways Group 21(1): 50-6	- Comparator in study does not match that specified in this review protocol *Study compared SMART therapy to usual care - not a relevant comparator in this review protocol*
Ringdal, N, Chuchalin, A, Chovan, L et al. (2002) Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microg bd Diskus vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. Respiratory medicine 96(11): 851-61	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA combination inhaler to ICS + ICS administered concurrently - not a relevant comparison in this review*
Ringdal, N, Eliraz, A, Pruzinec, R et al. (2003) The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. Respiratory medicine 97(3): 234-41	- Comparator in study does not match that specified in this review protocol *Study compared low-dose ICS plus montelukast to low-dose ICS/LABA combination - not a relevant comparator in this review*
Robinson, D S; Campbell, D; Barnes, P J (2001) Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. Lancet (London, England) 357(9273): 2007-11	- Inadequate study duration *Study treated participants for 2 weeks per treatment - inadequate duration to assess outcomes listed in this protocol*
Rodrigo, Gustavo J and Castro-Rodriguez, Jose A (2015) Tiotropium for the treatment of adolescents with moderate to severe symptomatic asthma: a systematic review with meta-analysis. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 115(3): 211-6	- Duplicate reference
Rodrigo, Gustavo J and Castro-Rodriguez, Jose A (2015) What is the role of tiotropium in asthma?: a systematic review with meta-analysis. Chest 147(2): 388-396	- No additional studies identified through reference checking
Rodrigo, Gustavo J, Moral, Vicente Plaza, Marcos, Luis Garcia et al. (2009) Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma. A systematic review. Pulmonary pharmacology & therapeutics 22(1): 9-19	- More recent systematic review included that covers the same topic

Study	Code [Reason]
Rodrigo, Gustavo J and Neffen, Hugo (2017) Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: A systematic review. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 28(6): 573-578	- No additional studies identified through reference checking
Rodrigo, Gustavo J and Plaza, Vicente (2016) Once-daily fluticasone furoate and vilanterol for adolescents and adults with symptomatic asthma: A systematic review with meta-analysis. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 116(6): 565-70	- No additional studies identified through reference checking
Rodriguez-Martinez, Carlos E; Sossa-Briceno, Monica P; Garcia-Marcos, Luis (2022) Use of inhaled corticosteroids on an intermittent or as-needed basis in pediatric asthma: a systematic review of the literature. The Journal of asthma : official journal of the Association for the Care of Asthma 59(11): 2189-2200	- Study does not contain an intervention relevant to this review protocol *Intermittent ICS in addition to SABA/FABA studied*
Rogliani, Paola, Cavalli, Francesco, Chetta, Alfredo et al. (2022) Potential Drawbacks of ICS/LABA/LAMA Triple Fixed-Dose Combination Therapy in the Treatment of Asthma: A Quantitative Synthesis of Safety Profile. Journal of asthma and allergy 15: 565-577	- Systematic review used as source of primary studies
Rogliani, Paola; Ritondo, Beatrice Ludovica; Calzetta, Luigino (2021) Triple therapy in uncontrolled asthma: a network meta-analysis of phase III studies. The European respiratory journal 58(3)	- No additional studies identified through reference checking
Rogliani, Paola, Ritondo, Beatrice Ludovica, Ora, Josuel et al. (2020) SMART and as-needed therapies in mild-to-severe asthma: a network meta-analysis. The European respiratory journal 56(3)	- No additional studies identified through reference checking
Rooklin, A, Elkayam, D, Weiler, J et al. (2001) The Fluticasone Propionate/Salmeterol HFA MDI is significantly more efficacious in treating asthma that placebo HFA Mdi, Fluticasone Propionate CFC MDI or Salmeterol CFC MDI. Journal of allergy and clinical immunology 107(2): 100	- Conference abstract

Study	Code [Reason]
Rosenhall, L, Elvstrand, A, Tilling, B et al. (2003) One-year safety and efficacy of budesonide/formoterol in a single inhaler (Symbicort Turbuhaler) for the treatment of asthma. Respiratory medicine 97(6): 702-8	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA combination inhaler to ICS + ICS administered concurrently - not a relevant comparison in this review*
Rosenhall, L, Heinig, J H, Lindqvist, A et al. (2002) Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. International journal of clinical practice 56(6): 427-33	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA combination inhaler to ICS + ICS administered concurrently - not a relevant comparison in this review*
Rosenhall, L, Heinig, JH, Lindqvist, A et al. (2001) Budesonide and formoterol in a single inhaler is safe and effective in the treatment of asthma. European respiratory journal 18(suppl33): 159s	- Conference abstract
Rosenhall, L, Heinig, JH, Lindqvist, A et al. (2001) Symbicort (Budesonide/eformoterol in a single inhaler) is safe and effective in the treatment of asthma. Thorax 56(suppl3): iii63	- Conference abstract
Rosenhall, L, Stahl, E, Heinig, JH et al. (2001) Health-related quality of life and asthma control in patients treated with budesonide and formoterol in a single inhaler. European respiratory journal 18(suppl33): 46s	- Conference abstract
Rowe, Brian H, Wong, Eric, Blitz, Sandra et al. (2007) Adding long-acting beta-agonists to inhaled corticosteroids after discharge from the emergency department for acute asthma: a randomized controlled trial. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 14(10): 833-40	- Study does not contain an intervention relevant to this review protocol *All study treatments were in addition to oral prednisone - not an intervention in this review*
Russell, G, Williams, D A, Weller, P et al. (1995) Salmeterol xinafoate in children on high dose inhaled steroids. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 75(5): 423-8	- Comparator in study does not match that specified in this review protocol *Study compared adding LABA to current ICS treatment vs placebo - not a relevant comparator in this review protocol*
Saeed, R; Mustafa, K; U Saqib, N (2018) Comparison of montelukast with fluticasone for control of Asthma in children. Medical forum monthly 29(3): 25-28	- Full text paper not available

Study	Code [Reason]
Saito, T. and Hasunuma, T. (2011) Safety and tolerability of high-dose budesonide/formoterol via turbuhaler in Japanese patients with asthma: Phase III study results. American Journal of Respiratory and Critical Care Medicine 183(1meetingabstracts)	- Conference abstract
Saito, Takefumi and Hasunuma, Tomoko (2012) Safety and Tolerability of High-Dose Budesonide/Formoterol via Turbuhaler R in Japanese Patients with Asthma : A Randomized, Double-Blind, Crossover, Active Comparator-Controlled, Phase III Study. Clinical drug investigation 32(1): 51-61	- Inadequate study duration *Study treated participants for 2 weeks per treatment - inadequate duration to assess outcomes listed in this protocol*
Saleh, C., Kim, L., Whalen-Browne, A. et al. (2020) TRIPLE THERAPY (ICS/LABA/LAMA) IN PATIENTS WITH UNCONTROLLED ASTHMA: A SYSTEMATIC REVIEW AND META-ANALYSIS. Annals of Allergy, Asthma and Immunology 125(5supplement): 37-s38	- Conference abstract
Salvi, S., Vaidya, A., Kodgule, R. et al. (2016) A randomized, double-blind study comparing the efficacy and safety of a combination of formoterol and ciclesonide with ciclesonide alone in asthma subjects with moderate-to-severe airflow limitation. Lung India 33(3): 272-277	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA with low-dose ICS (80 mcg ciclesonide twice daily) - low-dose ICS not a relevant intervention in this review*
Salvi, Sundeep S, Vaidya, Abhijit J, Kodgule, Rahul R et al. (2016) A randomized, double-blind study comparing the efficacy and safety of a combination of formoterol and ciclesonide with ciclesonide alone in asthma subjects with moderate-to-severe airflow limitation. Lung India : official organ of Indian Chest Society 33(3): 272-7	- Duplicate reference
Sanchez, D.A. and Louisias, M. (2023) Reduced Asthma Exacerbations by the Addition of Inhaled Corticosteroids to Rescue Therapy in Black and Latinx Adults. Journal of Allergy and Clinical Immunology: In Practice 11(3): 968-969	- Comparator in study does not match that specified in this review protocol *Study compared addition of ICS to usual care - not a protocol specified comparator*
Schmidt, H., Moroni-Zentgraf, P., Engel, M. et al. (2016) Once-daily tiotropium respimat add-on to at least ICS maintenance therapy in patients with symptomatic asthma: Methodology of modeling analyses by serum IgE and blood eosinophil levels. Journal of Allergy and Clinical Immunology 137(2suppl1): ab212	- Conference abstract

Study	Code [Reason]
Schmidt, O., Hamelmann, E., Vogelberg, C. et al. (2016) Efficacy, safety and tolerability of once-daily tiotropium Respimat add-on therapy in children with moderate symptomatic asthma. Thorax 71(supplement3): a167-a168	- Conference abstract
Sears, M R, Boulet, L-P, Laviolette, M et al. (2008) Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma. The European respiratory journal 31(5): 982-9	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA with conventional best practice - not a relevant comparator in this review*
Sears, Malcolm R and Radner, Finn (2009) Safety of budesonide/formoterol maintenance and reliever therapy in asthma trials. Respiratory medicine 103(12): 1960-8	- Review article but not a systematic review
Shah, A R, Sharples, L D, Solanki, R N et al. (2006) Double-blind, randomised, controlled trial assessing controller medications in asthma. Respiration; international review of thoracic diseases 73(4): 449-56	- Inadequate study duration *Study treated participants for 8 weeks - inadequate duration to assess the outcomes listed in this review protocol*
Shah, Monil Bharat, Gohil, Jayendra, Khapekar, Swati et al. (2014) Montelukast versus budesonide as a first line preventive therapy in mild persistent asthma in 2 to 18 y. Indian journal of pediatrics 81(7): 655-9	- Population not relevant to this review protocol *Participants had asthma that was newly diagnosed*
Shapiro, G, Lumry, W, Wolfe, J et al. (2000) Combined salmeterol 50 microg and fluticasone propionate 250 microg in the diskus device for the treatment of asthma. American journal of respiratory and critical care medicine 161(2pt1): 527-34	- Conference abstract
Shatalina, S., Geppe, N., Denisova, A. et al. (2017) Intermittent therapy with budesonide/formoterol in children with moderate asthma. European Respiratory Journal 50(supplement61)	- Conference abstract
Sheffer, Albert L, Silverman, Mike, Woolcock, Ann J et al. (2005) Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 94(1): 48-54	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*

Study	Code [Reason]
Shrewsbury, S; Pyke, S; Britton, M (2000) Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ (Clinical research ed.) 320(7246): 1368-73	- No additional studies identified through reference checking
Sienra Monge, JJL, Del Rio, BE, Alvarez, ME et al. (2001) Comparisaon of quality of life and pulmonary function on moderate asthmatic children treated with Beclomethasone and Beclomethasone plus Salmeterol. Journal of allergy and clinical immunology 107(2): 263	- Conference abstract
Simons, F E, Villa, J R, Lee, B W et al. (2001) Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. The Journal of pediatrics 138(5): 694-8	- Inadequate study duration *Study treated participants with therapies for 4 weeks per treatment - inadequate for the outcomes specified in this review protocol*
Sims, Erika J; Jackson, Catherine M; Lipworth, Brian J (2003) Add-on therapy with montelukast or formoterol in patients with the glycine-16 beta2-receptor genotype. British journal of clinical pharmacology 56(1): 104-11	- Inadequate study duration *Study treated participants for 2 weeks per treatment - inadequate duration to assess outcomes listed in this review protocol*
Singh, D., Bailes, Z., Barnes, N. et al. (2021) CAPTAIN:Improvements in airflow obstruction in patients with uncontrolled asthma. European Respiratory Journal 58(suppl65)	- Conference abstract
Singh, D., Virchow, J., Cononica, W. et al. (2021) Persistent airflow limitation and the risk for moderate-severe asthma exacerbations: A post-hoc analysis of the trimaran and trigger studies. American Journal of Respiratory and Critical Care Medicine 203(9)	- Conference abstract
Singh, D., Virchow, J.C., Canonica, W.G. et al. (2019) Characteristics of prominent response to triple therapy in patients with asthma uncontrolled on ICS/LABA: A stratified analysis of the TRIMARAN and TRIGGER studies. European Respiratory Journal 54(supplement63)	- Conference abstract
Singh, D., Virchow, J.C., Canonica, W.G. et al. (2021) Effect of high ics dose fixed combination Extrafine beclomethasone dipropionate, Formoterol fumarate, and glycopyrronium (bdp/ff/g) pmdi on asthma control in patients with persistent airflow limitation (pal): A posthoc	- Conference abstract

Study	Code [Reason]
Analysis of the trigger study. Thorax 76(suppl1): a19-a20	
Singh, Dave, Virchow, Johann Christian, Canonica, Giorgio Walter et al. (2020) Determinants of response to inhaled extrafine triple therapy in asthma: analyses of TRIMARAN and TRIGGER. Respiratory research 21(1): 285	- Secondary publication of an included study that does not provide any additional relevant information
Skoner, David P, Meltzer, Eli O, Milgrom, Henry et al. (2011) Effects of inhaled mometasone furoate on growth velocity and adrenal function: a placebo-controlled trial in children 4-9 years old with mild persistent asthma. The Journal of asthma : official journal of the Association for the Care of Asthma 48(8): 848-59	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Sobieraj, Diana M, Weeda, Erin R, Nguyen, Elaine et al. (2018) Association of Inhaled Corticosteroids and Long-Acting beta-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. JAMA 319(14): 1485-1496	- Systematic review used as source of primary studies
Soes-Petersen, Ulrik, Kava, Tuomo, Dahle, Ragnar et al. (2011) Budesonide/formoterol maintenance and reliever therapy versus conventional best standard treatment in asthma in an attempted 'real life' setting. The clinical respiratory journal 5(3): 173-82	- Comparator in study does not match that specified in this review protocol *Comparator was conventional best standard treatment, which was varied between participants*
Sorkness, Christine A, Lemanske, Robert F Jr, Mauger, David T et al. (2007) Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. The Journal of allergy and clinical immunology 119(1): 64-72	- Population not relevant to this review protocol *Participants could have been receiving additional therapies other than ICS and bronchodilators at screening*
Spahn, Joseph D, Covar, Ronina A, Jain, Neal et al. (2006) Effect of montelukast on peripheral airflow obstruction in children with asthma. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 96(4): 541-9	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Spears, M, Donnelly, I, Jolly, L et al. (2009) Effect of low-dose theophylline plus beclometasone on lung function in smokers with asthma: a pilot study. The European respiratory journal 33(5): 1010-7	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*

Study	Code [Reason]
Spector, S.L., Martin, U.J., Uryniak, T. et al. (2010) Effect of budesonide/formoterol pressurized metered-dose inhaler versus budesonide dry powder inhaler on asthma control in black adolescents and adults with moderate to severe persistent asthma. Annals of Allergy, Asthma and Immunology 105(5): a45	- Conference abstract
Spector, S.L., Martin, U.J., Uryniak, T. et al. (2010) Effect of budesonide/formoterol pressurized metered-dose inhaler vs budesonide dry powder inhaler on pulmonary function in black adolescents and adults with moderate to severe persistent asthma. Chest 138(4)	- Conference abstract
Spector, S.L., O'Brien, C.D., Uryniak, T. et al. (2010) Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler in non-black and black populations with moderate to severe persistent asthma. Annals of Allergy, Asthma and Immunology 105(5): a45-a46	- Conference abstract
Spector, S.L., O'Brien, C.D., Uryniak, T. et al. (2010) Safety and tolerability of a budesonide/formoterol (BUD/FM) pressurized metered-dose inhaler (PMDI) in black adolescents and adults with moderate to severe persistent asthma. Chest 138(4)	- Conference abstract
Stallberg, B, Ekstrom, T, Neij, F et al. (2008) A real-life cost-effectiveness evaluation of budesonide/formoterol maintenance and reliever therapy in asthma. Respiratory medicine 102(10): 1360-70	- Comparator in study does not match that specified in this review protocol *Study compared regular plus as-needed ICS/formoterol to low-moderate dose ICS (100-400 mcg) and formoterol (4.5 or 9 mcg) administered concurrently or to regular low-moderate dose ICS/formoterol (80/4.5 or 160/4.5 mcg, two inhalations twice daily), with dose dependent upon pre-trial ICS dose - low-dose ICS/LABA combinations are not a relevant intervention in this review*
Stankovic, IJ, Djordjevic, DV, Pejcic, TA et al. (2000) Formoterol and beclomethasone dipropionate versus higher dose beclomethasome dipropionate in asthma patients. European respiratory journal 16(suppl31): 455s	- Conference abstract
Stauffer, J, Yancey, S, Waitkus-Edwards, K et al. (2004) Clinical markers of worsening asthma	- Conference abstract

Study	Code [Reason]
with the fluticasone/salmeterol 100/50mcg Diskus FSC vs fluticasone propionate (FP) 250mcg alone in patients requiring FP 250mcg BID for asthma stability. Annals of allergy, asthma and immunology 92(1): 144	
Steinfeld, J.; Yiu, G.; Miller, S.D. (2015) Dose-ranging study to evaluate the efficacy and safety of four doses of fluticasone propionate/salmeterol multidose dry powder inhaler (FS MDPI) compared with fluticasone propionate (FP) MDPI and FS DPI in subjects with persistent asthma. Journal of Allergy and Clinical Immunology 135(2suppl1): ab6	- Conference abstract
Stelmach, I; Jerzynska, J; Kuna, P (2002) A randomized, double-blind trial of the effect of glucocorticoid, antileukotriene and beta-agonist treatment on IL-10 serum levels in children with asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 32(2): 264-9	- Inadequate study duration *Study treated participants for 8 weeks - inadequate duration to assess the outcomes listed in this review protocol*
Stelmach, Iwona, Grzelewski, Tomasz, Bobrowska-Korzeniowska, Monika et al. (2007) A randomized, double-blind trial of the effect of anti-asthma treatment on lung function in children with asthma. Pulmonary pharmacology & therapeutics 20(6): 691-700	- Inadequate study duration *Study treated participants for 8 weeks - inadequate duration to assess outcomes in this review protocol*
Stelmach, Iwona, Grzelewski, Tomasz, Majak, Pawel et al. (2008) Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma. The Journal of allergy and clinical immunology 121(2): 383-9	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Stelmach, Iwona, Majak, Pawel, Jerzynska, Joanna et al. (2004) Comparative effect of triamcinolone, nedocromil and montelukast on asthma control in children: A randomized pragmatic study. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 15(4): 359-64	- Inadequate study duration *Study treated participants for 8 weeks - inadequate duration to assess the outcomes listed in this review protocol*
Stempel, D.A., Raphiou, I., Kral, K. et al. (2016) Austri, a large randomized study in adolescents and adults with asthma, assessing the safety and efficacy of salmeterol in combination with fluticasone propionate compared to fluticasone propionate alone. Journal of Allergy and Clinical Immunology 137(2suppl1): ab389	- Conference abstract

Study	Code [Reason]
Stempel, D.A., Raphiou, I.H., Kral, K.M. et al. (2016) A 6-month safety and benefit study of inhaled fluticasone propionate/salmeterol combination vs inhaled fluticasone propionate in the treatment of subjects 4-11 years old with persistent asthma. Allergy: European Journal of Allergy and Clinical Immunology 71(supplement102): 604	- Conference abstract
Stempel, D, Szefler, S, Pedersen, S et al. (2016) Safety of salmeterol/fluticasone propionate (FSC) compared to fluticasone propionate (FP) in 4-17 yr olds with asthma. European respiratory journal 48(suppl60): oa4798	- Conference abstract
Stempel, David A, Raphiou, Ibrahim H, Kral, Kenneth M et al. (2016) Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone. The New England journal of medicine 374(19): 1822-30	- Population not relevant to this review protocol *Participants could have been receiving therapies other than ICS and bronchodilators at screening*
Stempel, David A, Szefler, Stanley J, Pedersen, Soren et al. (2016) Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma. The New England journal of medicine 375(9): 840-9	- Population not relevant to this review protocol *Participants could have been receiving therapies other than ICS and bronchodilators at screening*
Stojkovic Andjelkovic, AK, Pajovic, DM, Protrka, OJ et al. (2001) Effect of combination fluticasone propionate and salmeterol diskhaler in treatment of moderate to severe asthma: comparison of initial high dose, constant moderate dose and placebo. European respiratory journal 18(suppl33): 123s	- Conference abstract
Storms, William, Chervinsky, Paul, Ghannam, Asma F et al. (2004) A comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge. Respiratory medicine 98(11): 1051-62	- Inadequate study duration *Study treated participants for 4 weeks - inadequate duration to assess outcomes in this review protocol*
Strauch, Elke, Moske, Olaf, Thoma, Sandra et al. (2003) A randomized controlled trial on the effect of montelukast on sputum eosinophil cationic protein in children with corticosteroid-dependent asthma. Pediatric research 54(2): 198-203	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Suessmuth, Sandra; Freihorst, Joachim; Gappa, Monika (2003) Low-dose theophylline in	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
childhood asthma: a placebo-controlled, double-blind study. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 14(5): 394-400	*Intervention was ICS + theophylline - not relevant for this population (children)*
Svedsater, H., Jacques, L., Powell, D. et al. (2019) Reduced prescriptions of salbutamol in patients initiated on fluticasone furoate/vilanterol (FF/VI) compared with continuing usual care (UC) in the asthma salford lung study (SLS Asthma). American Journal of Respiratory and Critical Care Medicine 199(9)	- Conference abstract
Svedsater, H., Stynes, G., Wex, J. et al. (2014) Treatment efficacy of once-daily fluticasone furoate/vilanterol (FF/VI) is comparable with twice-daily combination therapies in asthma: A mixed treatment comparison. Value in Health 17(3): a170	- Conference abstract
Svedsater, Henrik, Jones, Rupert, Bosanquet, Nick et al. (2018) Patient-reported outcomes with initiation of fluticasone furoate/vilanterol versus continuing usual care in the Asthma Salford Lung Study. Respiratory medicine 141: 198-206	- Comparator in study does not match that specified in this review protocol *Comparator was usual care - not a relevant comparator in this review*
Szefler, Stanley J, Baker, James W, Uryniak, Tom et al. (2007) Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. The Journal of allergy and clinical immunology 120(5): 1043-50	- Secondary publication of an included study that does not provide any additional relevant information *Secondary publication (Szefler 2013) with direct infant population included*
Szefler, Stanley J, Phillips, Brenda R, Martinez, Fernando D et al. (2005) Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. The Journal of allergy and clinical immunology 115(2): 233-42	- Inadequate study duration *Study treated participants for 8 weeks per treatment - inadequate duration for the outcomes listed in this review protocol*
Szefler, Stanley J, Vogelberg, Christian, Bernstein, Jonathan A et al. (2019) Tiotropium Is Efficacious in 6- to 17-Year-Olds with Asthma, Independent of T2 Phenotype. The journal of allergy and clinical immunology. In practice 7(7): 2286-2295e4	- Comparator in study does not match that specified in this review protocol *Study compared ICS plus LAMA to placebo - not a relevant comparator in this review*
Tal, A, Simon, G, Vermeulen, J H et al. (2002) Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma. Pediatric pulmonology 34(5): 342-50	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*

Study	Code [Reason]
Tal, A, Simon, G, Vermeulen, JH et al. (2001) Rapid and sustained improvements in lung function and symptom control with budesonide/ formoterol in adolescent asthma. European respiratory journal 18(suppl33): 494s	- Conference abstract
Tanaka, A., Ohta, S., Yamamoto, M. et al. (2017) Tolerability of as-needed treatment with budesonide and formoterol combination in adult patients with mild asthma. American Journal of Respiratory and Critical Care Medicine 195	- Conference abstract
Tashkin, D., Chipps, B., Brown, R. et al. (2013) Responder analysis evaluating the long-term treatment of budesonide/formoterol pressurized metered-dose Inhaler (BUD/FM pMDI) in patients with moderate to severe asthma with versus without fixed airflow obstruction (FAO). Chest 144(4meetingabstract)	- Conference abstract
Tashkin, D., Chipps, B., Uryniak, T. et al. (2012) Asthma control and study withdrawal in patients with versus without fixed airflow obstruction (2 criteria): Post HOC analysis of a budesonide/formoterol pressurized metered-dose inhaler study in patients with moderate to severe asthma. Chest 142(4suppl1)	- Conference abstract
Tashkin, D., Moroni-Zentgraf, P., Engel, M. et al. (2014) Once-daily tiotropium respimat add-on to ICS+LABA reduces risk of severe exacerbation and asthma worsening in patients with asthma, independent of degree of airflow obstruction. Chest 146(4meetingabstract)	- Conference abstract
Tashkin, D.P., Chipps, B.E., Uryniak, T. et al. (2012) Effect of fixed airflow obstruction on response to budesonide/formoterol pressurized metered-dose inhaler treatment in African-American adolescents and adults with moderate to severe asthma. American Journal of Respiratory and Critical Care Medicine 185(meetingabstracts)	- Conference abstract
Tashkin, D.P., Moroni-Zentgraf, P., Engel, M. et al. (2013) Once-daily tiotropium reduces risk of exacerbations and asthma worsening in patients with symptomatic asthma despite treatment with inhaled corticosteroids and long-acting beta2-agonists. Chest 144(4meetingabstract)	- Conference abstract

Study	Code [Reason]
Thoma, S (2002) Anti-inflammatory effect of montelukast on corticosteroid-dependent children with asthma. Universitat freiburg	- Conference abstract
Thomas, B. (2014) Effect of step up therapy on bronchial hyperresponsiveness in children with poorly controlled asthma on inhaled corticosteroid (ICS) monotherapy. Pediatric Pulmonology 49(suppl37): 50-s51	- Conference abstract
Timmer, Wolfgang, Moroni-Zentgraf, Petra, Cornelissen, Piet et al. (2015) Once-daily tiotropium Respimat(R) 5 mug is an efficacious 24-h bronchodilator in adults with symptomatic asthma. Respiratory medicine 109(3): 329-38	- Inadequate study duration *Study treated participants for 4 weeks per treatment - inadequate duration for the outcomes in this review protocol*
Tinkelman, D G, Reed, C E, Nelson, H S et al. (1993) Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. Pediatrics 92(1): 64-77	- Comparator in study does not match that specified in this review protocol *Study compared regular ICS to theophylline - not a relevant intervention in this review*
Tomlinson, J E M, McMahon, A D, Chaudhuri, R et al. (2005) Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. Thorax 60(4): 282-7	- Comparator in study does not match that specified in this review protocol *Study compared low-dose ICS (400 mcg budesonide) to high-dose ICS (2000 mcg budesonide) - not a relevant comparator in this review*
Tong, Xiang, Liu, Tao, Li, Zhenzhen et al. (2021) Is It Really Feasible to Use Budesonide-Formoterol as Needed for Mild Persistent Asthma? A Systematic Review and Meta-Analysis. Frontiers in pharmacology 12: 644629	- Study does not contain an intervention relevant to this review protocol *Review assesses use of as needed ICS/LABA, not regular*
Turpeinen, M, Nikander, K, Pelkonen, A S et al. (2008) Daily versus as-needed inhaled corticosteroid for mild persistent asthma (The Helsinki early intervention childhood asthma study). Archives of disease in childhood 93(8): 654-9	- Comparator in study does not match that specified in this review protocol *Study compared regular low-dose ICS to higher dose ICS and disodium cromoglycate - neither of which are relevant comparators in this review*
Ukena, D, Harnest, U, Sakalauskas, R et al. (1997) Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. The European respiratory journal 10(12): 2754-60	- Study does not contain an intervention relevant to this review protocol *Theophylline was not a specified treatment in this review*
Vaessen-Verberne, Anna A P H, van den Berg, Norbert J, van Nierop, Jan C et al. (2010) Combination therapy salmeterol/fluticasone	- Duplicate reference

Study	Code [Reason]
versus doubling dose of fluticasone in children with asthma. American journal of respiratory and critical care medicine 182(10): 1221-7	
van Adelsberg, Janet, Moy, James, Wei, Lynn X et al. (2005) Safety, tolerability, and exploratory efficacy of montelukast in 6- to 24-month-old patients with asthma. Current medical research and opinion 21(6): 971-9	- Comparator in study does not match that specified in this review protocol *Study compared montelukast to placebo - not a relevant comparator in this review protocol*
Van den Berg, N J, Ossip, M S, Hederos, C A et al. (2000) Salmeterol/fluticasone propionate (50/100 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in children with asthma. Pediatric pulmonology 30(2): 97-105	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA combination inhaler to ICS + ICS administered concurrently - not a relevant comparison in this review*
van der Molen, T, Postma, D S, Turner, M O et al. (1997) Effects of the long acting beta agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. The Netherlands and Canadian Formoterol Study Investigators. Thorax 52(6): 535-9	- Comparator in study does not match that specified in this review protocol *Study compared adding LABA to usual ICS to continuing usual therapy with a placebo added - not a relevant comparator for this review*
van der Molen, T, Sears, M R, de Graaff, C S et al. (1998) Quality of life during formoterol treatment: comparison between asthma-specific and generic questionnaires. Canadian and the Dutch Formoterol Investigators. The European respiratory journal 12(1): 30-4	- Comparator in study does not match that specified in this review protocol *Study compared adding LABA to usual ICS to continuing usual therapy with a placebo added - not a relevant comparator for this review*
van Noord, J A, Schreurs, A J, Mol, S J et al. (1999) Addition of salmeterol versus doubling the dose of fluticasone propionate in patients with mild to moderate asthma. Thorax 54(3): 207-12	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA to increasing ICS dose alone with dose stratified based on pre-trial ICS dose - lower dose strata was not moderate-high dose ICS as required for this review*
Van Noord, J.A., Lill, H., Carrillo Diaz, T. et al. (2001) Clinical equivalence of a salmeterol/fluticasone propionate combination product (50/500mug) delivered via a chlorofluorocarbon-free metered-dose inhaler with the DiskusTM in patients with moderate to severe asthma. Clinical Drug Investigation 21(4): 243-255	- Data not reported in an extractable format or a format that can be analysed *Continuous data reported without variance, dichotomous data not grouped per treatment*
Van Schayck, C., Buhl, R., Haughney, J. et al. (2010) Budesonide/Formoterol maintenance and reliever therapy at two different maintenance doses. American Journal of	- Conference abstract

Study	Code [Reason]
Respiratory and Critical Care Medicine 181(1meetingabstracts)	
van Zyl-Smit, R., Krull, M., Gessner, C. et al. (2019) Efficacy and long-term safety of QMF149 (indacaterol acetate/mometasone furoate) versus mometasone furoate and versus salmeterol xinafoate/fluticasone propionate in patients with inadequately-controlled asthma: The PALLADIUM study. Thorax 74(supplement2): a210-a211	- Conference abstract
Van Zyl-Smit, R., Lawrence, D., Mezzi, K. et al. (2022) Efficacy of once-daily (o.d.) indacaterol/glycopyrronium/mometasone (IND/GLY/MF) vs free combination of twice-daily salmeterol/fluticasone (SAL/FLU) & o.d. tiotropium with respect to age, age at asthma-onset & BMI at baseline: ARGON subgroup analysis. European Respiratory Journal 60(supplement66)	- Conference abstract
van Zyl-Smit, R.N., Chapman, K.R., Kerstjens, H.A.M. et al. (2023) Mometasone/Indacaterol/Glycopyrronium (MF/IND/GLY) and MF/IND at Different MF Strengths versus Fluticasone Propionate/ Salmeterol Xinafoate (FLU/SAL) and FLU/SAL+ Tiotropium in Patients with Asthma. Journal of Asthma and Allergy 16: 123-134	- Secondary publication of an included study that does not provide any additional relevant information
van Zyl-Smit, R.N., Kerstjens, H.A.M., Maspero, J. et al. (2023) Triple Therapy with Mometasone/Indacaterol/Glycopyrronium or Doubling the ICS/LABA Dose in GINA Step 4: IRIDIUM Analyses. Pulmonary Therapy 9(3): 395-409	- Secondary publication of an included study that does not provide any additional relevant information
Van Zyl-Smit, Richard N, Kerstjens, Huib Am, Maspero, Jorge F et al. (2023) Efficacy of once-daily, single-inhaler, fixed-dose combination of mometasone/indacaterol/glycopyrronium in patients with asthma with or without persistent airflow limitation: Post hoc analysis from the IRIDIUM study. Respiratory medicine 211: 107172	- Secondary publication of an included study that does not provide any additional relevant information
Vandewalker, M., Bisgaard, H., Harper, T. et al. (2018) Safety and efficacy of tiotropium respimat add-on therapy in pre-school children with symptomatic persistent asthma. Pediatrics 141(1)	- Conference abstract

Study	Code [Reason]
Vandewalker, M., Harper III, T., Moroni-Zentgraf, P. et al. (2015) Once-daily tiotropium respimat add-on therapy improves lung function in adolescent patients with moderate symptomatic asthma, independent of t helper 2 inflammatory status. Annals of Allergy, Asthma and Immunology 115(5suppl1): a54-a55	- Conference abstract
Vandewalker, M., Harper, T., Moroni-Zentgraf, P. et al. (2015) Once-daily tiotropium respimat add-on to inhaled corticosteroids over 1 year improves lung function in adolescent patients with moderate symptomatic asthma, independent of patients baseline characteristics. Chest 148(4meetingabstract)	- Conference abstract
Vandewalker, M., Meltzer, E., Engel, M. et al. (2014) Safety and tolerability of oncedaily tiotropium respimat addon to at least ICS: Results from five phase III trials in adult patients with symptomatic asthma. Chest 146(4meetingabstract)	- Conference abstract
Vandewalker, M., Vogelberg, C., Hamelmann, E. et al. (2017) Tiotropium respimat add-on therapy improves lung function in adolescents and children with moderate symptomatic asthma, irrespective of IgE levels and eosinophil count. American Journal of Respiratory and Critical Care Medicine 195	- Conference abstract
Vandewalker, M.L., Hamelmann, E., Engel, M. et al. (2017) Once-daily tiotropium respimat add-on therapy has a safety profile comparable with placebo in children and adolescents. Journal of Allergy and Clinical Immunology 139(2supplement1): ab94	- Conference abstract
Vandewalker, M.L., Karpel, J., Bensch, G. et al. (2014) Once-daily tiotropium Respimat add-on to maintenance therapy improves lung function in patients with moderate or severe symptomatic asthma, independent of T helper 2 inflammatory status. Annals of Allergy, Asthma and Immunology 113(5suppl1): a105-a106	- Conference abstract
Vaquerizo, M J, Casan, P, Castillo, J et al. (2003) Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. Thorax 58(3): 204-10	- Comparator in study does not match that specified in this review protocol *Study compared addition of placebo or montelukast to current ICS therapy - placebo is not a comparator in this review protocol*

Study	Code [Reason]
Venugopal, S. (2019) Effect of addition of single dose of oral montelukast to standard therapy in acute moderate asthma in children 5-12 years of age-a randomised double blind placebo controlled trial. American Journal of Respiratory and Critical Care Medicine 199(9)	- Conference abstract
Verberne, A A, Frost, C, Duiverman, E J et al. (1998) Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. The Dutch Asthma Study Group. American journal of respiratory and critical care medicine 158(1): 213-9	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Verberne, A A, Frost, C, Roorda, R J et al. (1997) One year treatment with salmeterol compared with beclomethasone in children with asthma. The Dutch Paediatric Asthma Study Group. American journal of respiratory and critical care medicine 156(3pt1): 688-95	- Duplicate reference
Verberne, A.A.P.H., Frost, C., Roorda, R.J. et al. (1997) One year treatment with salmeterol compared with beclomethasone in children with asthma. American Journal of Respiratory and Critical Care Medicine 156(3i): 688-695	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Vermetten, F A, Boermans, A J, Luiten, W D et al. (1999) Comparison of salmeterol with beclomethasone in adult patients with mild persistent asthma who are already on low-dose inhaled steroids. The Journal of asthma : official journal of the Association for the Care of Asthma 36(1): 97-106	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Virchow, J., Singh, D., Canonica, W.G. et al. (2021) Normalization of airflow obstruction with extra fine beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) pmdi: A post-hoc analysis of the trimaran and trigger studies. American Journal of Respiratory and Critical Care Medicine 203(9)	- Conference abstract
Virchow, J.C., Canonica, W., Paggiaro, P. et al. (2019) Reducing the rate of severe asthma exacerbations using singleinhaler extrafine BDP/FF/GB combination compared to BDP/FF in patients with uncontrolled asthma: Pooled results from the TRIMARAN and TRIGGER studies. American Journal of Respiratory and Critical Care Medicine 199(9)	- Conference abstract

Study	Code [Reason]
Virchow, J.C., Paggiaro, P., Canonica, W.G. et al. (2019) Effect of extrafine moderate strength (MS) ICS-containing triple therapy on exacerbations in asthmatics with persistent airflow limitation: A post-hoc analysis of the TRIMARAN study. European Respiratory Journal 54(supplement63)	- Conference abstract
Vogelberg, C., Engel, M., Moroni-Zentgraf, P. et al. (2014) O05-Once-daily tiotropium in adolescents with symptomatic asthma despite inhaled corticosteroid treatment: A dose-ranging study. Clinical and Translational Allergy 4(suppl1): 5dummy	- Conference abstract
Vogelberg, C., Hamelmann, E., Szefler, S.J. et al. (2017) Once-daily tiotropium respimat add-on therapy improves lung function and control in adolescents and children with moderate symptomatic asthma. Journal of Allergy and Clinical Immunology 139(2supplement1): ab95	- Conference abstract
Vogelberg, C., Hamelmann, E., Vrijlandt, E.J.L.E. et al. (2018) Tiotropium add-on therapy has a safety profile comparable with that of placebo in children and adolescents with symptomatic asthma. Pediatrics 142(1)	- Conference abstract
Vogelmeier, C; Naya, I; Ekelund, J (2012) Budesonide/formoterol maintenance and reliever therapy in Asian patients (aged >=16 years) with asthma: a sub-analysis of the COSMOS study. Clinical drug investigation 32(7): 439-49	- Secondary publication of an included study that does not provide any additional relevant information
Vrijlandt, Elianne J L E, El Azzi, Georges, Vandewalker, Mark et al. (2018) Safety and efficacy of tiotropium in children aged 1-5 years with persistent asthmatic symptoms: a randomised, double-blind, placebo-controlled trial. The Lancet. Respiratory medicine 6(2): 127-137	- Study does not contain an intervention relevant to this review protocol *ICS + LAMA not a treatment listed in this review protocol for <5s*
Walsh, J and Murphy, DM (2019) Combination inhaled corticosteroid/long acting beta agonist therapy- an evolving role in asthma care. Irish medical journal 112(2): 864	- Review article but not a systematic review
Wang, Gang, Zhang, Xin, Zhang, Hong Ping et al. (2017) Corticosteroid plus beta2-agonist in a single inhaler as reliever therapy in intermittent and mild asthma: a proof-of-concept systematic	- No additional studies identified through reference checking

Study	Code [Reason]
review and meta-analysis. Respiratory research 18(1): 203	
Wang, Liqun; Zhou, Ruirui; Xie, Xiaohui (2019) Tiotropium added to low- to moderate-dose inhaled corticosteroids (ICS) versus low- to moderate-dose ICS alone for adults with mild to moderate uncontrolled persistent asthma: A systematic review and meta-analysis. The Journal of asthma : official journal of the Association for the Care of Asthma 56(1): 69-78	- No additional studies identified through reference checking
Wang, Yan, Chen, Ping, Dai, Anna et al. (2016) Intervention Studies of Inhaled Corticosteroids Combined with Long-acting Theophylline or Long-acting beta2-agonists in Patients with Moderate to Severe Asthma: A Randomized, Controlled Study. Clinical therapeutics 38(12): 2622-2627e1	- Comparator in study does not match that specified in this review protocol *Theophylline is not a treatment listed in this review protocol*
Wang, Yan, Lin, Kexiong, Wang, Changzheng et al. (2011) Addition of theophylline or increasing the dose of inhaled corticosteroid in symptomatic asthma: a meta-analysis of randomized controlled trials. Yonsei medical journal 52(2): 268-75	- Study does not contain an intervention relevant to this review protocol *Theophylline is not a treatment listed in this review protocol*
Wang, Yan, Wang, Chang-Zheng, Lin, Ke-Xiong et al. (2005) Comparison of inhaled corticosteroid combined with theophylline and double-dose inhaled corticosteroid in moderate to severe asthma. Respirology (Carlton, Vic.) 10(2): 189-95	- Comparator in study does not match that specified in this review protocol *Study compared regular ICS to ICS plus theophylline - theophylline is not a relevant intervention in this review*
Watz, H., Hohlfeld, J.M., Singh, D. et al. (2019) The combination of indacaterol/glycopyrronium/mometasone furoate is superior to high-dose salmeterol/fluticasone propionate in improving lung function in patients with asthma. American Journal of Respiratory and Critical Care Medicine 199(9)	- Conference abstract
Weatherall, M., Holliday, M., Baggott, C. et al. (2019) Combined analysis of two randomized controlled trials of budesonide/formoterol reliever therapy in adults with mild asthma. Thorax 74(supplement2): a212	- Conference abstract
Wechsler, Michael E, Szefler, Stanley J, Ortega, Victor E et al. (2019) Step-Up Therapy in Black Children and Adults with Poorly Controlled Asthma. The New England journal of medicine 381(13): 1227-1239	- Population not relevant to this review protocol *Participants had received therapies other than ICS and bronchodilators*

Study	Code [Reason]
Weersink, E J, Douma, R R, Postma, D S et al. (1997) Fluticasone propionate, salmeterol xinafoate, and their combination in the treatment of nocturnal asthma. American journal of respiratory and critical care medicine 155(4): 1241-6	- Population not relevant to this review protocol *Participants could have received additional medication other than ICS and bronchodilators prior to inclusion*
Weersink, E J, van Zomeren, E H, Koeter, G H et al. (1997) Treatment of nocturnal airway obstruction improves daytime cognitive performance in asthmatics. American journal of respiratory and critical care medicine 156(4pt1): 1144-50	- Population not relevant to this review protocol *Participants could have received additional medication other than ICS and bronchodilators prior to inclusion*
Wei, Zhengbo and Li, Sheng (2023) An efficacy and safety evaluation of montelukast + fluticasone propionate vs. fluticasone propionate in the treatment of cough variant asthma in children: a meta-analysis. BMC pulmonary medicine 23(1): 489	- Population not relevant to this review protocol *The children did not receive glucocorticoids, leukotriene antagonists, antihistamines, or other drugs within one month before the start of the study. So treatment naive and trying ICS Vs ICS+Montelukast. Doesn't fit either 3.1 or 3.2 protocols because montelukast not in 3.1 protocol, and it's not step-up from ICS (first line treatment) so not 3.2. Paper does not report anything on asthma control.*
Weinstein, S., Nathan, R., Meltzer, E. et al. (2012) Reduction in asthma deteriorations in subjects with persistent asthma not well controlled on low-, moderate-, or high-dose inhaled corticosteroids: A pooled analysis from three clinical trials using combined mometasone furoate/formoterol. World Allergy Organization Journal 5(suppl2): 79	- Conference abstract
Weinstein, S.F., Berger, W.E., Noonan, M. et al. (2009) Prevention of asthma worsening with inhaled mometasone furoate therapy in children. Journal of Allergy and Clinical Immunology 123(2suppl1): 66	- Conference abstract
Weinstein, S.F., Nathan, R.A., Meltzer, E.O. et al. (2011) Reduction in asthma deteriorations in subjects with persistent asthma uncontrolled on low-, moderate-, or high-dose inhaled corticosteroids: A pooled analysis from three clinical trials using combined mometasone furoate/formoterol. Journal of Allergy and Clinical Immunology 127(2suppl1): ab86	- Conference abstract
Weinstein, S.F.; Nathan, R.A.; Nolte, H. (2010) Combined mometasone furoate/formoterol reduces asthma deteriorations in patients with	- Conference abstract

Study	Code [Reason]
persistent asthma uncontrolled on moderate- or high-dose inhaled corticosteroids. Annals of Allergy, Asthma and Immunology 105(5): a51-a52	
Weinstein, SF, Pearlman, DS, Condemi, JJ et al. (2001) Superior efficacy of the fluticasone propionate/salmeterol 88/42mcg HFA-MDI combination product versus the individual components in asthmatics previously treated with either short- or long-acting beta2-agonists or inhaled corticosteroids. Journal of allergy and clinical immunology 107(2): 102abstract339	- Conference abstract
Weinstein, SF, Pearlman, DS, Condemi, JJ et al. (2001) Superior efficacy of the Fluticasone Propionate/Salmeterol (88/42MCG) Hfa-Mdi combination product versus the individual components in asthmatics previously treated with either short or long-acting Beta2-agonist or inhaled corticosteroids. Journal of allergy and clinical immunology 107(2): 102	- Conference abstract
Weinstein, Steven F, Corren, Jonathan, Murphy, Kevin et al. (2010) Twelve-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids. Allergy and asthma proceedings 31(4): 280-9	- Population not relevant to this review protocol *Participants had severe asthma, not within the scope of this guideline*
Wennergren, G., Stallberg, B., Lofdahl, C. et al. (2009) Budesonide/formoterol maintenance and reliever therapy - lower corticosteroid load in the treatment of asthma in adolescents. Allergy: European Journal of Allergy and Clinical Immunology 64(suppl90): 73	- Conference abstract
Whalen-Browne, A., Kim, L., Saleh, C. et al. (2022) Triple therapy (LAMA, ICS and LABA) in asthma control in patients with uncontrolled, persistent asthma: a systematic review and meta-analysis. Allergy, Asthma and Clinical Immunology 18(suppl1)	- Conference abstract
White, M., Meltzer, E.O., Nathan, R.A. et al. (2010) Improved asthma control with mometasone furoate/formoterol: A new combination treatment for persistent asthma. Annals of Allergy, Asthma and Immunology 105(5): a49-a50	- Conference abstract

Study	Code [Reason]
White, M., Nolte, H., Meltzer, E. et al. (2010) Asthma symptom control using a combination of mometasone furoate/Formoterol (MF/F): Grouped analysis of three clinical trials. Journal of Allergy and Clinical Immunology 125(2suppl1): ab194	- Conference abstract
White, M., Nolte, H., Meltzer, E.O. et al. (2010) Mometasone furoate/formoterol improves asthma control in subjects with uncontrolled persistent asthma. Respirology 15(suppl2): 59	- Conference abstract
White, M.V., Nolte, H., Meltzer, E.O. et al. (2010) Mometasone furoate/formoterol improves asthma control in subjects with uncontrolled persistent asthma. Chest 138(4)	- Conference abstract
White, M, Scott, C, Herrle, MR et al. (2001) Salmeterol/fluticasone propionate 42/88mcg hfa-mdi improves asthma control in asthmatics previously treated with short- or long-acting beta2-agonists or inhaled corticosteroids. Annals of allergy, asthma & immunology 86: 81	- Conference abstract
White, MV, Shapiro, G, Taylor, J et al. (1999) The salmeterol xinafoate/fluticasone propionate dry powder combination product via diskus r inhaler improves asthma control compared to the individual products in patients previously treated with inhaled corticosteroids. American journal of respiratory and critical medicine 159(3): a635	- Conference abstract
Williams, B, Noonan, G, Reiss, T F et al. (2001) Long-term asthma control with oral montelukast and inhaled beclomethasone for adults and children 6 years and older. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 31(6): 845-54	- Secondary publication of an included study that does not provide any additional relevant information *Secondary analysis of three studies excluded from this review*
Wilson, A M, Dempsey, O J, Sims, E J et al. (2001) Evaluation of salmeterol or montelukast as second-line therapy for asthma not controlled with inhaled corticosteroids. Chest 119(4): 1021-6	- Inadequate study duration *Study treated participants for two weeks per treatment - inadequate to assess outcomes in this review protocol*
Wilson, AM, Dempsey, OJ, Sims, EJ et al. (1999) A comparison of salmeterol and montelukast as second-line therapy in asthmatic patients not controlled on inhaled corticosteroids. Thorax: a66p189	- Duplicate reference

Study	Code [Reason]
Woolcock, A, Lundback, B, Ringdal, N et al. (1996) Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. American journal of respiratory and critical care medicine 153(5): 1481-8	- Comparator in study does not match that specified in this review protocol *Study compared moderate-high dose ICS to LABA monotherapy (50 or 100 mcg salmeterol)*
Wyrwich, Kathleen W, Ireland, Andrea M, Navaratnam, Prakash et al. (2011) An assessment of change in asthma control among adolescents and adults with persistent asthma in mometasone furoate/formoterol fumarate clinical trials. The Journal of asthma : official journal of the Association for the Care of Asthma 48(1): 48-56	- Population not relevant to this review protocol *Secondary analysis of studies that included participants without uncontrolled asthma*
Xie, Z, Chai, M, Gu, W et al. (2021) Effects of montelukast combined with budesonide on lung function and exhaled nitric oxide concentration in children with mild persistent asthma. International journal of clinical and experimental medicine 14(4): 1814-1820	- Comparator in study does not match that specified in this review protocol *Study compared montelukast to nasal budesonide - not a relevant treatment in this review*
Yi, Fang, Zhan, Chen, Liu, Baojuan et al. (2022) Effects of treatment with montelukast alone, budesonide/formoterol alone and a combination of both in cough variant asthma. Respiratory research 23(1): 279	- Inadequate study duration *Study treated participants for 8 weeks - inadequate duration to assess outcomes specified in this review protocol*
Yildirim, Z; Ozlu, T; Bulbul, Y (2001) Montelukast and budesonide vs double dose budesonide in moderate asthma. European respiratory journal 18(suppl33): 261s	- Conference abstract
Yildirim, Zeki, Ozlu, Tevfik, Bulbul, Yilmaz et al. (2004) Addition of montelukast versus double dose of inhaled budesonide in moderate persistent asthma. Respirology (Carlton, Vic.) 9(2): 243-8	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Yoshihara, S, Fukuda, H, Tamura, M et al. (2016) Efficacy and Safety of Salmeterol/fluticasone Combination Therapy in Infants and Preschool Children with Asthma Insufficiently Controlled by Inhaled Corticosteroids. Drug research 66(7): 371-376	- Study design not relevant to this review protocol *Observational study, not an RCT*
Yoshihara, Shigemi, Tsubaki, Toshikazu, Ikeda, Masanori et al. (2019) The efficacy and safety of fluticasone/salmeterol compared to fluticasone in children younger than four years of age. Pediatric allergy and immunology : official	- Inadequate study duration *Randomised treatment period was 8 weeks - inadequate duration to assess outcomes in this protocol*

Study	Code [Reason]
publication of the European Society of Pediatric Allergy and Immunology 30(2): 195-203	
You-Ning, L, Humphries, M, Du, X et al. (2005) Efficacy and safety of salmeterol/fluticasone propionate delivered via a hydrofluoroalkane metered dose inhaler in Chinese patients with moderate asthma poorly controlled with inhaled corticosteroids. International journal of clinical practice 59(7): 754-9	- Inadequate study duration *Study treated participants for 4 weeks - inadequate duration to assess the outcomes in this review protocol*
Yurdakul, Ahmet Selim, Taci, Nevin, Eren, Aysegul et al. (2003) Comparative efficacy of once-daily therapy with inhaled corticosteroid, leukotriene antagonist or sustained-release theophylline in patients with mild persistent asthma. Respiratory medicine 97(12): 1313-9	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Zangrilli, J., McElhattan, J., O'Brien, C.D. et al. (2009) Predose and postdose forced expiratory flow between 25% and 75% (FEF25-75%) in adolescents and adults with asthma treated with twice-daily budesonide/formoterol pressurized Metered-Dose Inhaler (BUD/FM pMDI) or BUD pMDI for 1 year. Journal of Allergy and Clinical Immunology 123(2suppl1): 79	- Conference abstract
Zangrilli, J.; Uryniak, T.; O'brien, C.D. (2009) Efficacy of budesonide/formoterol (BUD/FM) vs BUD in Hispanic patients: Differential results when including run-in lung function vs controller history and run-in symptoms. Annals of Allergy, Asthma and Immunology 103(5suppl3): a61	- Conference abstract
Zeiger, Robert S, Bird, Steven R, Kaplan, Michael S et al. (2005) Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. The American journal of medicine 118(6): 649-57	- Population not relevant to this review protocol *Participants were not receiving ICS at study entry*
Zetterstrom, O, Buhl, R, Mellem, H et al. (2000) The new single inhaler product containing both budesonide/formoterol improves asthma control in adults. European respiratory journal 16(suppl31): 455s	- Conference abstract
Zhang, Li, Huang, Guangyin, Jin, Long et al. (2018) Therapeutic Effects of a Long-Acting Cholinergic Receptor Blocker, Tiotropium Bromide, on Asthma. Medical science monitor : international medical journal of experimental and clinical research 24: 944-950	- No relevant outcomes identified *study treatment duration was 8 weeks - inadequate duration to assess the outcomes specified in this review protocol*

Study	Code [Reason]
Zhang, Shiyuan, King, Denise, Rosen, Virginia M et al. (2020) Impact of Single Combination Inhaler versus Multiple Inhalers to Deliver the Same Medications for Patients with Asthma or COPD: A Systematic Literature Review. International journal of chronic obstructive pulmonary disease 15: 417-438	- No additional studies identified through reference checking
Zhang, Y., Wang, H., Cao, M. et al. (2020) The efficacy of montelukast combined with budesonide in asthma patients and the combination's effects on the patients' immune and pulmonary functions. International Journal of Clinical and Experimental Medicine 13(11): 8194-8205	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Zhang, Y and Li, B (2020) Effects of montelukast sodium plus budesonide on lung function, inflammatory factors, and immune levels in elderly patients with asthma. Irish journal of medical science 189(3): 985-990	- Population not relevant to this review protocol *Participants did not have asthma that was uncontrolled*
Zhong, N., Barnes, N., Gibbs, M. et al. (2015) Inhaled salmeterol/fluticasone propionate is more effective than fluticasone propionate alone at achieving total asthma control in Asian patients: A post hoc analysis of the goal study. Respirology 20(suppl3): 13	- Conference abstract
Zhong, Nan Shan, Ping, Zheng Jin, Humphries, Michael J et al. (2004) Salmeterol/Fluticasone Propionate in a Single Inhaler is Superior to Budesonide Alone in Control of Chinese Asthmatic Adults : An Open-Label, Randomised, 6-Week Study. Clinical drug investigation 24(10): 583-92	- Inadequate study duration *Study treated participants for 6 weeks - inadequate duration to assess outcomes listed in this review protocol*
Zhou, W.; Ke, H.X.; Li, Y. (2015) Effect of nebulized corticosteroids on long-term poorly controlled asthma in elderly patients. Journal of the American Geriatrics Society 63(suppl2): 390	- Conference abstract
Zhou, Xiao-Jian, Qin, Zhen, Lu, Jiao et al. (2021) Efficacy and safety of salmeterol/fluticasone compared with montelukast alone (or add-on therapy to fluticasone) in the treatment of bronchial asthma in children and adolescents: a systematic review and meta-analysis. Chinese medical journal 134(24): 2954-2961	- No additional studies identified through reference checking

Study	Code [Reason]
Zimmerman, Barry; D'Urzo, Anthony; Berube, Denis (2004) Efficacy and safety of formoterol Turbuhaler when added to inhaled corticosteroid treatment in children with asthma. Pediatric pulmonology 37(2): 122-7	- Comparator in study does not match that specified in this review protocol *Study compared ICS/LABA to usual ICS plus placebo - not a comparison listed in this review protocol*

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 20: Studies excluded from the health economic review

Reference	Reason for exclusion
Main 2008(Main et al., 2008)	Excluded as rated not applicable. Cost comparison analysis using costs from 2006 considered too out-dated to be applicable to the current setting.
Tamminen 2008(Tamminen et al., 2008)	Selectively excluded as this is a cost effectiveness analysis based on an RCT by Kuna 2007 from Finnish HC perspective with 2006 costs. This analysis does not add any additional evidence to the included cost effectiveness analysis presented in Wickstrom 2009 (Danish perspective, 2007 costs applied), also based on Kuna 2007.
Miller 2008(Miller et al., 2008)	Selectively excluded as this is a cost effectiveness analysis based on an RCT by Kuna 2007 from Canadian HC perspective with 2006 costs applied. This analysis does not add any additional evidence to the included cost effectiveness analysis presented in Wickstrom 2009 (Danish perspective, 2007 costs applied), also based on Kuna 2007.
Miller 2007(Miller et al., 2007)	Selectively excluded as this is a cost effectiveness analysis based on an RCT by Vogelmeir 2005 from Canadian HC perspective with 2005 costs applied. This analysis was excluded due to costs being older than 15 year cut off outlined in protocol and an a cost effectiveness analysis has already been included based on this RCT in Wickstrom 2009 (Danish perspective, 2007 costs applied).
Buendia 2021A(Buendia et al., 2021)	Excluded as rated not applicable. Colombian societal perspective used. Healthcare perspective not extractable.
Buendia 2021B(Buendia et al., 2021)	Excluded as rated not applicable. Colombian societal perspective used. Healthcare perspective not extractable.
Buendia 2022(Buendia et al., 2022)	Excluded as rated not applicable. Colombian societal perspective used. Healthcare perspective not extractable.
Buendia 2023(Antonio Buendia et al., 2023)	Excluded as rated not applicable. Colombian societal perspective used. Healthcare perspective not extractable.

Appendix K Research recommendation

K.1.1 Research recommendation

To compare different add-on strategies for adults who need additional treatment after initial treatment with ICS/formoterol used PRN (as required).

K.1.2 Why this is important

Asthma is a common condition affecting around 1 in 12 adults in the UK. There are a number of different therapeutic interventions for people with asthma who are not controlled with ICS/formoterol on an as-required basis. It is important to investigate the safety and effectivity of different add-on medications for adults needing additional treatment.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Asthma is a common condition in adults and can cause increased morbidity and mortality.
Relevance to NICE guidance	Relevant to NICE Asthma Guidance
Relevance to the NHS	In the UK, asthma causes thousands of emergency hospital attendances and several deaths every year. There is significant burden on affected people, their families and the healthcare economy.
National priorities	High
Current evidence base	Low quality evidence
Equality considerations	None known

K.1.4 Modified PICO table

Population	Adults with asthma in the UK. Setting: Primary, Secondary and Tertiary Care.
Intervention	Add-on treatments to ICS/formoterol as required
Comparator	Different add-on treatments and/or standard care
Outcome	Reduction in asthma exacerbations and hospital admissions
Study design	RCT or Cross-sectional study design
Timeframe	Long term
Additional information	None